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(54) **PERFORMANCE MONITORING OF REGIONAL CITRATE ANTICOAGULATION**

LEISTUNGSÜBERWACHUNG EINER REGIONALEN CITRAT-ANTIKOAGULATION

SURVEILLANCE DE PERFORMANCE DE L'ANTICOAGULATION RÉGIONALE AU CITRATE

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(73) Proprietor: **Gambro Lundia AB**

226 43 Lund (SE)

(72) Inventors:

• **HOBRO, Sture
226 47 Lund (SE)**

• **ALSON, Jonas**

222 40 Lund (SE)

• **NILSSON, Anders**

247 35 Södra Sandby (SE)

• **FORSAL, Innas**

214 45 Malmö (SE)

(74) Representative: **Sweden SHS IP Office**

Gambro Lundia AB

P.O. Box 10101

220 10 Lund (SE)

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EP 3 893 959 B1

DescriptionTechnical Field

5 **[0001]** The present invention relates to regional citrate anticoagulation (RCA) during blood treatment, and in particular to a technique for performance monitoring during a blood treatment that involves RCA, e.g. a continuous or semi-continuous renal replacement therapy.

Background Art

10 **[0002]** Continuous or semi-continuous renal replacement therapies have become established as the treatment of choice for supporting critically ill patients with acute kidney injury. Continuous renal replacement therapy (CRRT) is typically a 24-hour treatment, whereas semi-continuous therapy may be performed daily with a duration of 6-12 hours or more. There are many different forms or "modalities" of continuous or semi-continuous renal replacement therapies, including but not limited to CVVH (continuous veno-venous hemofiltration), CVVHD (continuous veno-venous hemodialysis), CVVHDF (continuous veno-venous hemodiafiltration), SLEF (slow extended hemofiltration), SLED (sustained low-efficiency dialysis), and SCUF (slow continuous ultrafiltration). Common to these therapies is that they operate with a relatively low blood flow rate in the extracorporeal blood circuit, typically less than 200 ml/min. Renal replacement therapy involves passing the patient's blood through plastic tubings and membranes (e.g. in a dialyzer), which triggers clotting as well as complement cascade. Continuous and semi-continuous therapies usually require some degree of anticoagulation to prevent clotting in the extracorporeal blood circuit. Without anticoagulation, the survival of tubings and membranes is diminished and therapy becomes less effective.

25 **[0003]** Citrate or citric acid ($C_6H_8O_7$) is present in the human plasma, among other forms, as a trivalent negative citrate anion. This ion chelates ionized calcium (Ca^{2+}) in the plasma resulting in a single negative calcium-citrate complex and in low levels of free ionized calcium. Since the coagulation cascade requires free ionized calcium for optimal function, blood clotting in the extracorporeal blood circuit may be prevented by infusion of citrate into the withdrawal (arterial) limb of the extracorporeal blood circuit. As citrate is a small molecule, a majority of the calcium-citrate complex is moved across the membrane of the dialyzer and is lost in the dialysate effluent. To replace lost calcium, a local infusion of free ionized calcium is made into the return (venous) limb of the extracorporeal blood circuit or directly into the patient. Theoretically, this type of Regional Citrate Anticoagulation, commonly abbreviated RCA or CRA, is both very powerful and fully reversible without systemic (intra-patient) bleeding tendencies.

30 **[0004]** However, RCA has a potential for causing electrolyte abnormalities. Reported derangements by RCA include metabolic alkalosis and acidosis, hypernatremia and hyponatremia, and hypocalcemia. Such abnormalities are detected with proper monitoring and the local treatment protocol should describe how to adjust fluid flows under different conditions to counteract or prevent the abnormalities. The incidence of metabolic complications depends on the amount of citrate administered, the design, rules and flexibility of the protocol, and its proper use.

35 **[0005]** During RCA, it is common practice to measure the calcium blood status in two locations; a first location representing the blood in the patient and a second location with the highest risk of clotting. Depending on the local treatment protocol, the first location may be in the patient or at an upstream end of the extracorporeal blood circuit, resulting in "systemic" measurement values, and the second location may be upstream or downstream the dialyzer in the extracorporeal blood circuit, resulting in "pre-dialyzer" and "post-dialyzer" measurement values, respectively. The concentration of ionized calcium at the second location is monitored to ensure a low risk for coagulation in the extracorporeal blood circuit and may be used for modifying citrate dose accordingly. The level of systemic ionized calcium (at the first location) is monitored to ensure that the calcium infusion is capable of maintaining systemic ionized calcium levels within physiological range and may be used for modifying calcium infusion rate accordingly. For example, a target value for post-dialyzer ionized calcium may be in the range 0.3-0.5 mmol/L and a target value for systemic ionized calcium may be in the range 1.1-1.25 mmol/L.

40 **[0006]** One serious and potentially life-threatening complication of RCA is citrate accumulation in the patient. In clinical practice, the total-to-ionized calcium ratio (aka calcium ratio), which is related to the blood citrate concentration, is commonly accepted as an indirect index of citrate accumulation during RCA. For example, a calcium ratio ≥ 2.5 may imply an increased risk of metabolic complications. To enable evaluation of the calcium ratio, the total calcium in the patient (aka total systemic calcium or systemic total calcium) is monitored together with the systemic ionized calcium.

45 **[0007]** Thus, protocols for RCA typically prescribe monitoring of at least three calcium values, namely ionized calcium at the first and second locations and total calcium at the first location, and often one or more additional systemic blood parameters, such as pH, bicarbonate, potassium, serum sodium, etc. Ionized calcium may be measured by sampling and subsequent sample analysis, e. g. by a blood gas analyzer, where the sampling and sample analysis may be performed every 20 minutes at startup of RCA and then at least every 6 hours when stable conditions are attained. Systemic total calcium may be measured by a laboratory test of a blood sample and may be performed at least once daily.

[0008] Further details regarding RCA and its implementations and complications are found in the articles "Citrate anticoagulation for continuous renal replacement therapy (CRRT) in patients with acute kidney injury admitted to the intensive care unit", by Davenport and Tolwani, published in NDT Plus (2009) 2:439-447, and "Complication of regional citrate anticoagulation: accumulation or overload?", by Schneider et al., published in Critical Care (2017) 21:281.

[0009] RCA is known to be laborious, costly and complex, partly because of the need for frequent measurements of blood parameters, including ionized calcium. Further, conventional blood gas analyzers are typically not approved for typical concentrations of post-dialyzer ionized calcium (e.g. 0.2-0.5 mmol/L), nor for samples having high levels of citrate. Thus, it has been shown that the current practice of performing sampling and blood gas analysis may be afflicted by measurement errors, e.g. in the article "Discrepant post filter ionized calcium concentrations by common blood gas analyzers in CRRT using regional citrate anticoagulation" by Schwarzer et al., published in Critical Care (2015) 19:321.

[0010] There is a general need to improve the practice of using RCA during renal replacement therapy, with respect to at least one of simplicity, cost and accuracy.

[0011] The prior art comprises US2008/0015487 which proposes to install an online clearance monitor (OCM) for precise measurement of the delivered small solute clearance, and an online sensor system (OSS) for measuring free ionized levels of calcium, magnesium and citrate in the effluent fluid. It is further proposed to use the measurement values provided by the OSS to back-calculate the corresponding values in the patient's plasma. Allegedly, it is possible to mathematically derive the patient's plasma citrate and total calcium and magnesium level and thereby eliminate the need for laboratory monitoring of the patient's systemic total and ionized calcium and magnesium levels during RCA. However, the proposed use of an OCM and an OSS will not only add significant cost but also considerable complexity to the therapy, e.g. with respect to calibration and maintenance of the OCM and OSS.

[0012] WO2010/029401 presents a method for controlling, in continuous dialysis using RCA, the local infusion of calcium by calculations based on modeling of the reactions in the blood circulation, or by approximation of calcium clearance, in accordance with the actual flow rates and the mode of treatment. Specifically, it is proposed to control a pump for local infusion of a calcium solution as a function of the flow rate of blood entering the arterial line, the flow rate of effluent fluid from the dialyzer and the flow rate of citrate, while presuming a known concentration of the infused calcium solution and a fixed value of the systemic total calcium.

[0013] WO2010/148194 relates to conventional intermittent hemodialysis for patients suffering from chronic kidney disease (CKD) and proposes to perform RCA by combining infusion of citrate with the use of a dialysate containing both citrate and calcium, to thereby reduce or eliminate the need for post-dialyzer calcium infusion. A method is also proposed for blind prediction of the concentration of systemic ionized calcium at any point during the dialysis treatment or after completed dialysis treatment ("post-dialysis"), by use of a time-dependent mathematical model that includes processes in the patient affecting both calcium and citrate. The blind prediction implies that the systemic ionized calcium is blindly calculated as a function of time based solely on an initial measurement, e.g. at the start of dialysis treatment. There is no indication about the parameters that are measured in the initial measurement. The blind prediction involves computation of predicted concentrations of citrate and ionized calcium at various locations in the extracorporeal blood circuit. Since the mathematical model represents processes in the patient affecting calcium, it is further proposed to statistically correct the predicted concentration of post-dialysis systemic ionized calcium by accounting for the patient's parathyroid hormone (PTH) and/or alkaline phosphatase (AP) level. The correction is determined by employing a multivariate linear regression model including a category of the PTH or AP level of the patient, dialysis treatment time and the predicted concentration of post-dialysis systemic ionized calcium. A corresponding disclosure is found in the article "A Mathematical Model of Regional Citrate Anticoagulation in Hemodialysis", by Thijssen et al., published in Blood Purif 2010; 29:197-203.

[0014] Further relevant prior art is for instance disclosed in documents US9039647 B2, US2011/208105 A1 and US 2014/353251 A1.

Summary

[0015] It is an objective of the invention to at least partly overcome one or more limitations of the prior art.

[0016] A further objective is to improve the practice of using RCA during renal replacement therapy, with respect to at least one of simplicity, cost and accuracy.

[0017] One or more of these objectives, as well as further objectives that may appear from the description below, are at least partly achieved by a monitoring device, a blood treatment system, a method of monitoring, and a computer-readable medium, respectively according independent claims 1, 25, 26 and 27, embodiments thereof being defined by the dependent claims.

[0018] A first aspect of the invention is a monitoring device for a blood treatment system. The blood treatment system comprises an extracorporeal blood circuit which comprises a blood withdrawal line and a blood return line for connection to a vascular system of subject and a dialyzer intermediate the blood withdrawal and blood return lines. The blood treatment system is configured for regional citrate anticoagulation, RCA, by administration of citrate to the extracorporeal blood circuit upstream of the dialyzer during a treatment session. The monitoring device is configured to, at consecutive

time steps during the treatment session: obtain a current measurement value of systemic ionized calcium or systemic total calcium; operate a predefined algorithm on the current measurement value to generate a current computation value that represents ionized calcium in blood at a selected location downstream or upstream of the dialyzer in the extracorporeal blood circuit; and present and/or evaluate the current computation value for assessment of the regional citrate anticoagulation.

[0019] The first aspect makes it possible to dispense with or at least significantly reduce the need for the conventional procedure of taking and analyzing blood samples upstream and/or downstream of the dialyzer in the extracorporeal blood circuit. Instead, by the first aspect, corresponding information is obtained by algorithmic computations based on a measurement value of systemic ionized calcium or systemic total calcium. Such a measurement value may be obtained in accordance with conventional practice. Thus, the first aspect may serve to reduce the number blood samples that need to be taken and analyzed for monitoring the performance of the regional citrate anticoagulation. The complexity of performing blood treatment in combination with RCA is thereby reduced. Further, lowering the number of blood samples will free time for clinical staff as well as save expenditure for blood sample analysis. Although it may seem counter-intuitive, the accuracy of the computation value, at least when representing post-dialyzer ionized calcium, may even be better than the accuracy of the corresponding measurement value obtained by the conventional approach of performing blood sampling and subsequent blood sample analysis. As noted above, conventional blood gas analyzers are not optimized for blood that is sampled downstream of the dialyzer in the extracorporeal blood circuit and the resulting measurement value lacks in both accuracy and precision. On the other hand, there are established procedures and devices for measuring ionized and total calcium in the blood of the patient, i.e. systemic values, with high accuracy. Thus, by starting from a relatively accurate measurement value of systemic ionized calcium or systemic total calcium, it is not unlikely that the computation value produced by the first aspect is more accurate than the conventionally measured value.

[0020] The ability of the first aspect to provide a sufficient accuracy is also due to the fact that the current computation value is generated by operating the predefined algorithm on a current measurement value of systemic ionized calcium or systemic total calcium, e.g. a measurement value that is obtained anew to be relevant at the respective time step. Thereby, the computation starts from the actual level of ionized or total calcium in the subject's blood at each time step. Compared to using predicted levels of calcium in the extracorporeal blood circuit or the subject, the use of actual levels is more likely to render accurate results.

[0021] In the following, various embodiments of the first aspect are defined. These embodiments provide at least some of the technical effects and advantages described in the foregoing, as well as additional technical effects and advantages as readily understood by the skilled person, e.g. in view of the following detailed description.

[0022] In one embodiment, the monitoring device is further configured to obtain input data comprising current values of operation parameters of the blood treatment system, and optionally one or more of system configuration data for the blood treatment system, chemical parameter data for substances in the blood, and physiological parameter data for the subject, and the monitoring device is configured to operate the predefined algorithm on the input data and the current computation value to generate the current computation value.

[0023] In one embodiment, the predefined algorithm comprises a first function configured to estimate the ionized calcium in the blood at the selected location in the extracorporeal blood circuit, said first function being linearly dependent on total calcium at the selected location and total citrate at the selected location.

[0024] In one embodiment, the first function is obtained by linearization of a non-linear function with respect to each of total calcium and total citrate, wherein the non-linear function is a solution to a system of equations representing chemical reactions of calcium in free form and bound to other substances in blood, including citrate, while assuming predefined amounts of other substances than calcium and citrate.

[0025] In one embodiment, the linearization is performed with respect to reference values of total calcium and total citrate, said reference values corresponding to expected values of total calcium and total citrate, respectively, at the selected location.

[0026] In one embodiment, the predefined algorithm comprises a second function configured to estimate the total calcium in the blood at the selected location.

[0027] In one embodiment, the selected location is downstream of the dialyzer, and the second function depends on the systemic total calcium and represents a mass balance of total calcium that enters the extracorporeal blood circuit in the blood from the subject and total calcium in the blood at an intermediate location in the extracorporeal blood circuit upstream of the dialyzer, while accounting for fluid infusion into the extracorporeal blood circuit intermediate the subject and the intermediate location, wherein the second function further accounts for a loss of total calcium from the blood in the dialyzer.

[0028] In one embodiment, the predefined algorithm comprises a third function configured to estimate the total citrate in the blood at the selected location in the extracorporeal blood circuit.

[0029] In one embodiment, the selected location is downstream of the dialyzer, and the third function depends on systemic total citrate and represents a mass balance of total citrate that enters the extracorporeal blood circuit in the

blood from the subject and total citrate at an intermediate location in the extracorporeal blood circuit upstream of the dialyzer, while accounting for fluid infusion into the extracorporeal blood circuit intermediate the subject and the intermediate location, wherein the third function further accounts for a loss of total citrate from the blood in the dialyzer.

[0030] In one embodiment, the predefined algorithm further comprises a fourth function configured to estimate systemic total citrate as a function of time from start of the regional citrate anticoagulation.

[0031] In one embodiment, the fourth function represents a metabolic generation rate of citrate in the subject and further accounts for the administration of citrate into the extracorporeal blood circuit upstream of the dialyzer and a loss of total citrate from the blood in the dialyzer.

[0032] In one embodiment, the predefined algorithm further comprises at least one fifth function configured to estimate a clearance of total citrate and a clearance of total calcium from the blood in the dialyzer, wherein the monitoring device is configured to compute a loss of total citrate and a loss of total calcium in the dialyzer based on the clearance of total citrate and the clearance of total calcium, respectively.

[0033] In one embodiment, the predefined algorithm comprises a sixth function configured to estimate systemic total calcium as a function of the systemic ionized calcium.

[0034] In one embodiment, the predefined algorithm comprises a seventh function configured to estimate the systemic ionized calcium as a function of the systemic total calcium.

[0035] In one embodiment, the current measurement value represents the systemic ionized calcium in the blood of the subject, and the monitoring device is further configured to operate the predefined algorithm on the current measurement value to generate a further current computation value representing the systemic total calcium.

[0036] In an alternative embodiment, the current measurement value represents the systemic total calcium, and the monitoring device is further configured to operate the predefined algorithm on the current measurement value to generate a further current computation value representing the systemic ionized calcium.

[0037] In one embodiment, the monitoring device is further configured to operate the predefined algorithm to generate a further current computation value representing systemic total citrate.

[0038] In one embodiment, the monitoring device is further configured to evaluate at least the further current computation value for assessment of accumulation of citrate in the subject.

[0039] In one embodiment, the monitoring further comprises an interface for signal communication with a blood analysis apparatus, wherein the monitoring device is further configured to, at the respective consecutive time step, obtain the measurement value from a signal received over the interface from the blood analysis apparatus.

[0040] In one embodiment, the monitoring device is further configured to output the current computation value for presentation on a display device.

[0041] In one embodiment, the monitoring device is further configured to evaluate the current computation value for detection of an alarm situation, and cause an alarm to be generated when the alarm situation is detected.

[0042] In one embodiment, the monitoring device further comprises a decision support module, which is configured to evaluate the current computation value in relation to a clinically proven protocol for the regional citrate anticoagulation, obtain a recommendation for operation of the blood treatment system based on the protocol, and output the recommendation for presentation on a display device.

[0043] In one embodiment, the monitoring device further comprises an interface for signal communication with a set of pumping devices in the blood treatment system, wherein the monitoring device is further configured to generate one or more control signals for the set of pumping devices as a function of the current computation value, and provide the one of more control signals to the interface.

[0044] In one embodiment, the monitoring device is further configured, during the treatment session, to obtain measurement data representing at least one of calcium and citrate in the blood of the subject and/or the extracorporeal blood circuit, and adjust the predefined algorithm based on the measurement data.

[0045] A second aspect is a blood treatment system comprising an extracorporeal blood circuit for connection to a vascular system of a subject. The extracorporeal blood circuit comprises a blood withdrawal line and a blood return line for connection to the vascular system, and a dialyzer intermediate the blood withdrawal and blood return lines. The blood treatment system further comprises a pumping device for pumping blood from the subject through the blood withdrawal line, the dialyzer and the blood return line back to the subject. The blood treatment system further comprises a subsystem which is operable to perform regional citrate anticoagulation, RCA, in relation to the extracorporeal blood circuit and the subject, and a monitoring device in accordance the first aspect or any of its embodiments.

[0046] A third aspect of the invention is a method of monitoring a blood treatment system comprising an extracorporeal blood circuit which is configured for connection to a vascular system of a subject and comprises a dialyzer, wherein the blood treatment system is configured for regional citrate anticoagulation, RCA, by administration of citrate to the extracorporeal blood circuit upstream of the dialyzer during a treatment session. The method comprises, at consecutive time steps during the treatment session: obtaining a current measurement value of systemic ionized calcium or systemic total calcium; operating a predefined algorithm on the current measurement value to generate a current computation value representing ionized calcium in blood at a selected location downstream or upstream of the dialyzer in the extracorporeal

blood circuit; and presenting and/or evaluating the current computation value for assessment of the regional citrate anticoagulation.

[0047] Any one of the embodiments of the first aspect may be adapted and implemented as an embodiment of the third aspect.

[0048] A fourth aspect of the invention is a computer-readable medium comprising computer instructions which, when executed by a processor, cause the processor to perform the method of the third aspect and any of its embodiments.

[0049] Still other objectives, features, embodiments, aspects and advantages of the present invention may appear from the following detailed description, from the attached claims as well as from the drawings.

Brief Description of the Drawings

[0050] Embodiments of the invention will now be described in more detail with reference to the accompanying drawings.

FIG. 1 is a schematic overview of a CRRT system configured for use with RCA.

FIG. 2 corresponds to FIG. 1 and indicates machine parameters and locations for measurement and computation of calcium-related parameters during RCA monitoring.

FIG. 3 is a flow chart of an example method of RCA monitoring.

FIG. 4 is a block diagram of an example system for RCA monitoring.

FIG. 5 illustrates linearization of an extended function for calculating post-dialyzer ionized calcium.

FIG. 6 is a table of machine settings, physiological parameters, system parameters and chemical parameters for use in computations by the system in FIG. 4.

FIG. 7 is a flow chart of an example computation method performed by the system of FIG. 4.

FIGS 8A-8B show calculations of RCA-related parameters at a series of time steps based on concurrent measurements of systemic ionized calcium and systemic total calcium, respectively.

FIG. 9A is a graph of time averages of calculated and measured post-dialyzer ionized calcium for a plurality of patients, FIG. 9B is a graph of a time series of difference values between calculated and measured values of post-dialyzer ionized calcium for one patient, FIG. 9C is a graph of the time average of difference values between calculated and measured values of post-dialyzer ionized calcium for each of a plurality of patients, and FIG. 9D is a graph of the standard deviation of difference values between calculated and measured values of post-dialyzer ionized calcium for each of a plurality of patients.

FIG. 10 is an overview of functions that may be included in a predefined algorithm for use in RCA monitoring.

FIG. 11 is a flow chart of an alternative method of RCA monitoring.

Detailed Description of Example Embodiments

[0051] Embodiments of the present invention will now be described more fully hereinafter with reference to the accompanying drawings, in which some, but not all, embodiments of the invention are shown. Indeed, the invention may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, the invention is defined by the appended claims. Like numbers refer to like elements throughout. Where possible, any terms expressed in the singular form herein are meant to also include the plural form and/or vice versa, unless explicitly stated otherwise. As used herein, "at least one" shall mean "one or more" and these phrases are intended to be interchangeable. Accordingly, the terms "a" and/or "an" shall mean "at least one" or "one or more", even though the phrase "one or more" or "at least one" is also used herein. As used herein, except where the context requires otherwise owing to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, that is, to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

[0052] Embodiments of the disclosure are applicable to all forms of extracorporeal blood treatment or processing that may be combined with regional citrate anticoagulation (RCA), including acute dialysis therapies such as the continuous or semi-continuous renal replacement therapies discussed in the Background section, as well as chronic dialysis therapies such as intermittent hemodialysis, hemofiltration, hemodiafiltration and ultrafiltration etc, and hybrid dialysis therapies such as prolonged intermittent renal replacement therapy (PIRRT), sustained low-efficiency dialysis (SLED), and extended daily dialysis (EDD) etc. Conventionally, the different types of dialysis therapy are referred to as "modalities".

[0053] In the following, without limitation, embodiments will be described with reference to Continuous Renal Replacement Therapy (CRRT) and modalities thereof.

[0054] FIG. 1 is a schematic view of a blood treatment system 1 for performing CRRT in combination with RCA when connected to a human subject 100, denoted "patient" in the following. The system 1 comprises an extracorporeal blood circuit ("EC circuit") 10 which is connected to the vascular system of the patient 100 at a blood withdrawal end and a blood return end. The connections may be performed by any conventional device, such as a needle or catheter. Blood

lines or tubings are arranged to define a blood withdrawal path or limb 10a and a blood return path or limb 10b of the EC circuit 10. A blood filtration unit 11, denoted "dialyzer" herein, is connected between the withdrawal and return paths 10a, 10b. The dialyzer 11 comprises a semi-permeable membrane 11a, which is arranged to separate the dialyzer 11 into a blood compartment, which is fluidly connected to the withdrawal and return paths 10a, 10b, and a dialysis fluid compartment. A blood pump 12 is arranged in the withdrawal path 10a and is operable to draw blood from the patient 100 and pump the blood via the blood compartment of the dialyzer 11 and through the return path 10b back to the patient 100. The system 1 further comprises a source 13 of dialysis fluid. A dialysis fluid path or line 13a connects the source 13 to the dialysis fluid compartment of the dialyzer 11. Similarly, an effluent path or line 14a connects the dialysis fluid compartment of the dialyzer 11 to a sink 14 for spent dialysis fluid (denoted "effluent" in the following). A dialysis fluid pump 13b is arranged in the dialysis fluid path 13a, and an effluent pump 14b is arranged in the effluent path 14a.

[0055] In the illustrated example, the system 1 further comprises a first source 20 of replacement fluid which is connected by a first replacement fluid line 20a to the withdrawal path 10a intermediate the blood pump 12 and the dialyzer 11. A first replacement fluid pump 20b is arranged in the first replacement fluid line 20a. The system 1 further comprises a second source 21 of replacement fluid which is connected by a second replacement fluid line 21a to the return path 11a. A second replacement fluid pump 21b is arranged in the second replacement fluid line 21a.

[0056] The system 1 further comprises an arrangement for pre-dialyzer infusion of citrate into the EC circuit 10. The citrate infusion arrangement includes a source 22 of a citrate-containing fluid. A citrate fluid line 22a connects the source 22 to the withdrawal path 10a upstream of the blood pump 12. A citrate pump 22b is arranged in the citrate fluid line 22a.

[0057] The system 1 further comprises an arrangement for post-dialyzer infusion of ionized calcium into the EC circuit 10. The calcium infusion arrangement includes a source 23 of a calcium-containing fluid. In the illustrated example, a calcium fluid line 23a connects the source 23 to the return path 10b intermediate the dialyzer 11 and the second replacement fluid line 21a. In other examples, the line 23a may be connected to the return path 10b downstream of the second replacement fluid line 21a, or directly to the vascular system of the patient 100. In the illustrated example, the source 23 is a syringe pump which is operable to infuse the calcium-containing fluid. In an alternative, a separate calcium pump is arranged in the calcium fluid line 23a downstream of the source 23.

[0058] The system 1 is operated by a control device 40, which is configured to generate control signals S1-S7 for the pumps 12, 13b, 14b, 20b, 21b, 22b and 23 at least partly in accordance with a control program comprising computer instructions. The control program may also operate based on measurement signals received by the control device 40 from sensors (not shown) in the system 1. The control device 40 comprises a processor 41 and computer memory 42. The control program is stored in the memory 42 and executed by the processor 41. The control program may be supplied to the control device 40 on a computer-readable medium, which may be a tangible (non-transitory) product (e.g. magnetic medium, optical disk, read-only memory, flash memory, etc) or a propagating signal. In the illustrated example, the control device 40 comprises a control signal interface 43a for providing the control signals S1-S7 to the pumps in the system 1. The control device 40 also comprises an input interface 43b for connection to one or more input devices 44 that enables an operator to input control data, as well as an output interface 43c for connection to one or more output devices 45 for providing feedback data to the operator. For example, the input device(s) 44 may comprise a keyboard, keypad, computer mouse, control button, touch screen, printer, etc, and the output device(s) 45, may comprises a display device, an indicator lamp, an alarm device, etc. The operator may be a clinically experienced person, such as a physician or a nurse.

[0059] The control device 40 is operable to effect blood treatment in the system 1 by operating, in accordance with the control program, the pump 12 to circulate blood through the EC circuit 10, the pump 13b to supply dialysis fluid to the dialyzer 11, the pump 14b to remove effluent from the dialyzer 11, and the pumps 20a, 20b to infuse replacement fluid before the dialyzer 11 ("pre-infusion") and after the dialyzer 11 ("post-infusion"). The control device 40 is also operable to effect RCA in the system 1 by operating, in accordance with the control program, the pump 22b to infuse the citrate-containing fluid and the pump 23 to infuse the calcium-containing fluid. The underlying rationale for RCA and the infusion of citrate and calcium is described in the Background section and is also well-known to the person skilled in the art and will not be repeated here.

[0060] Although the system 1 in FIG. 1 is described for a modality that involves both dialysis, pre-infusion and post-infusion of replacement fluid, the system 1 may be modified into other modalities, e.g. by refraining from either of pre-infusion and post-infusion of replacement fluid, or both, and/or by performing pure ultrafiltration in the dialyzer 11 instead of dialysis. Further, embodiments of the invention are applicable to any clinically proven composition of the dialysis fluid, the replacement fluid, the citrate-containing fluid and the calcium-containing fluid, respectively.

[0061] FIG. 1 also indicates a conventional configuration of the system 1 for obtaining blood samples. As described in the Background section, in accordance with certain protocols, blood samples may be routinely taken to measure the level of systemic total calcium and systemic ionized calcium, as well as post-dialyzer ionized calcium. As used herein, "systemic" refers to the blood in the patient 100 and "ionized calcium" refers to the free calcium ions, Ca^{2+} . Further, the term "level" may be any type of relative or absolute measure, such as a concentration or an amount. In one non-limiting example, the post-dialyzer ionized calcium may be measured to monitor proper performance of anticoagulation, systemic

ionized calcium may be measured to monitor proper performance of the calcium infusion, and the systemic total calcium may be monitored to evaluate citrate accumulation in the patient 100. The systemic ionized calcium and post-dialyzer ionized calcium are conventionally measured in blood samples that are taken by connecting a respective sampling device 30a, 30b to the EC circuit 10 at a respective designated location. Specifically, systemic ionized calcium is measured at the upstream end of the withdrawal path 10a, i.e. close to the connection to the patient 100 where fresh blood enters the EC circuit 10. Post-dialyzer ionized calcium is measured in the return path 10b, downstream of the dialyzer 11 and upstream of the calcium infusion. When the sampling device 30a, 30b has been operated to obtain a blood sample, the sampling device 30a, 30b is disconnected from the EC circuit 10 and connected to a blood analysis apparatus 50, which is separate from the system 1 and configured to analyze the blood sample for determination of the level of ionized calcium, and possibly other blood parameters such as level of pH, bicarbonate, magnesium, sodium, potassium, chloride, hematocrit, oxygenation, etc. Any suitable blood analysis apparatus 50 may be used, e.g. a so-called blood gas analyzer (BGA).

[0062] Alternatively, the systemic ionized calcium may be measured by BGA analysis of a blood sample which is taken from the patient.

[0063] The systemic total calcium is conventionally measured by laboratory analysis of a blood sample which is taken from the patient or at a location in the EC circuit 10 close to the connection to the patient 100, e.g. by use of the sampling device 30a. The apparatus 50 may present the result of the analysis of the respective blood sample to the operator on a display device 51, whereupon the operator may evaluate the measurement values based on clinical experience and practice to decide if any setting needs to be changed. If so, the operator may change the setting(s) via the input device 44. Alternatively, as indicated by a dashed line in FIG. 1, the blood analysis apparatus 50 may be connected to transfer the measurement values over a wired or wireless connection 52 to the control device 40 via its input interface 43b, whereby the control device 40 may show the measurement values to the operator on the display 45.

[0064] FIG. 2 corresponds to FIG. 1 and shows the EC circuit 10 in linear outline, with blood from the patient entering at the left end and treated blood leaving at the right end. FIG. 2 also indicates parameters that may be used in computations in accordance with embodiments of the invention. The level of total calcium in the patient 100 is designated Ca_{SYS} ("systemic total calcium"), and the level of total citrate in the patient 100 is designated CIT_{SYS} ("total systemic citrate" or "systemic total citrate"). A first location at the upstream end of the EC circuit 10 is designated $loc1$ and the level of ionized calcium at $loc1$ is designated iCa_{SYS} ("systemic ionized calcium"). A second location downstream of the dialyzer 11 is designated $loc2$ and the level of ionized calcium at $loc2$ is designated iCa_2 ("post-dialyzer ionized calcium"). Further, the level of total citrate and total calcium at $loc2$ is designated CIT_2 ("post-dialyzer total citrate") and Ca_2 ("post-dialyzer total calcium"), respectively. A third location upstream of the dialyzer 11 and downstream of the citrate administration and the pre-infusion (if present) is designated $loc3$. It should be realized that $loc1$ and $loc2$ correspond to the sampling locations in FIG. 1. The flow rate of blood taken from the patient is designated by Q_B . Further, the flow rates of pumps in the system is designated by Q_D for the dialysis fluid pump 13b, Q_E for the effluent pump 14b, Q_{PRE} for the first replacement fluid pump 20b, Q_{POST} for the second replacement fluid pump 21b, Q_{PBP} for the citrate pump 22b, and Q_{SYR} for the calcium pump 23.

[0065] If the total or ionized calcium is measured at $loc1$, the measured values may differ slightly from the actual values in the patient, e.g. as a result of so-called access recirculation at the connection site where the arterial path 10a is connected to the vascular system. To compensate for the difference, a correction factor may be empirically or theoretically determined and applied to the measured values.

[0066] By insightful reasoning and thorough simulation and experimentation, the inventors have found that it is possible to replace at least the measurement of post-dialyzer ionized calcium, iCa_2 , by a computation of a corresponding parameter value based on a measurement value of either systemic total calcium, Ca_{SYS} , or systemic ionized calcium, iCa_{SYS} . Embodiments of the invention are based on this insight. The computation of iCa_2 will greatly reduce both cost and complexity of performing blood treatment in combination with RCA, since it obviates or at least reduces the need to regularly take blood samples downstream of the dialyzer 11 during blood treatment. As a conservative estimate, it takes at least 5 minutes for clinical staff to manually take the blood sample, transport the sampling device (30b in FIG. 1) to the blood analysis apparatus 50 and wait for the blood analysis. Assuming that 6-10 such samples are taken each day for each blood treatment machine, this corresponds to 30-50 minutes of qualified staff time. Further, the analysis of blood samples by the apparatus 50 also comes with an operational cost. Thus, for a clinic that operates a plurality of machines that perform blood treatment combined with RCA, considerable savings in both time and operational cost are enabled by embodiments of the invention.

[0067] FIG. 3 is a flow chart of a method 300 for performance monitoring of RCA during a blood treatment session in accordance with an embodiment. As used herein, a "blood treatment session" involves pumping blood through the EC circuit 11 when the latter has been arranged in fluid communication with the vascular system of the patient 100. The method 300 may be performed by the control program in the control device 40 (FIG. 1). Alternatively, the device 40 may be a dedicated monitoring device, whereas the control signals S1-S7 may be generated by a separate control device (not shown). In step 301, a current measurement value of systemic ionized calcium, iCa_{SYS} , or systemic total calcium,

Ca_{SYS} , is obtained. With reference to the device 40 in FIG. 1, a current measurement value of iCa_{SYS} may be obtained either by electronic transfer from the blood analysis apparatus 50 over communication line 52 or by the operator manually entering the measurement value through use of the input device 44. A current measurement value of Ca_{SYS} , which conventionally is given by a laboratory test, may be entered manually by the operator through use of the input device

44. In step 302, a current value of the post-dialyzer ionized calcium at $loc2$, i.e. iCa_2 (FIG. 2), is computed as a function of the current measurement value. Step 302 may involve operating a predefined algorithm on the current measurement value. It may be noted that step 301 may involve obtaining current measurement values of both iCa_{SYS} and Ca_{SYS} , and that step 302 may involve computing the current value of iCa_2 as a function of these current measurement values.

[0068] In step 303, the current value of iCa_2 is presented and/or evaluated for assessment of the RCA performance. For example, step 303 may involve presenting the current value of iCa_2 on a display device (cf. 45 in FIG. 1) or otherwise, to allow the operator to assess the RCA performance and take corrective action if deemed necessary. Alternatively or additionally, step 303 may involve a machine-implemented evaluation of the current value of iCa_2 for assessment of the RCA performance, which may result in, e.g., an alarm signal or a recommendation to the operator to change one or more settings of the system 1. Further examples of step 303 are given below with reference to FIG. 4. The method 300 then proceeds to step 304, in which it waits before returning to step 301. For example, step 304 may wait for a predefined time period, e.g. in accordance with a predefined sampling scheme as exemplified in the Background section. Alternatively, step 304 may proceed to step 301 whenever a new current measurement value of iCa_{SYS} or Ca_{SYS} is received by method 300.

[0069] From the flow chart in FIG. 3, it is seen that the computation of the current value of iCa_2 is based on a measurement value which is obtained anew for each repetition of steps 301-303. Thus, the computation of the current value of iCa_2 does not require the level of ionized or total calcium in the patient or in the EC circuit 10 to be projected over time. The skilled person realizes that the accuracy of the computed value is likely to increase when it is based on actual measurements rather than projections.

[0070] FIG. 4 is a block diagram of a system for RCA monitoring in accordance with an embodiment. Blocks 400-401 represent preparatory modeling and analysis for determining the predefined algorithm to be used in the RCA monitoring. Blocks 402-407 represent input data, and block 408 represents output data. Blocks 410 and 421-423 represent functional modules or processes that may be implemented in a monitoring device (cf. 40 in FIG. 1). In the following description of FIG. 4, reference is made to parameters that are defined in the nomenclature list at the end of the detailed description.

[0071] Block 400 involves defining an extended model of the system 1 and the patient 100 for the purpose of deriving an algorithm that defines the level of post-dialyzer ionized calcium. Such an extended model comprises a model of the relevant blood chemistry, including the interactions of calcium with other substances in the blood. The interactions are defined by a number of chemical reactions. The outcome of these reactions is determined by the local concentration of the reactants and chemical equilibrium constants together with the total amounts of calcium and other substances. The total of a substance is the sum of all its forms. The total concentrations depend on the composition of the blood that is pumped from the patient 100, the fluids that are mixed into the EC circuit 10, and the transport of substances over the membrane 11a. The blood chemistry includes calcium, both in free form and bound to other substances. In one example, the model of blood chemistry includes calcium in free form and calcium binding to citrate, albumin, bicarbonate, phosphate and carbonate, as well as substances that are competing to bind to citrate, albumin, bicarbonate, phosphate and carbonate, such as magnesium, sodium, and hydrogen. In embodiments of the invention, the concentration of calcium in the patient 100 is measured as total concentration (Ca_{SYS}) or as ionized (free) concentration (iCa_{SYS}). In one example, the model of blood chemistry assumes that the amount/concentration of the modeled substances other than calcium and citrate are known (e.g. measured or estimated) with the exception of citrate which is modeled over treatment time based on the known addition of citrate for anticoagulation (by pump 22b in FIG. 2). For example, the modeled substances other than calcium and citrate may be assumed to be constant over time.

[0072] In one example, the extended model quantifies each included reaction by its equilibrium constant (EQ), giving the equation: $([AB])/([A] \cdot [B]) = EQ$, where the complex AB is formed by A and B, and $[]$ denotes concentration.

[0073] The extended model accounts for the addition of fluids into the EC circuit 10 by considering the mass balance of each substance. Thus, the concentration of substance at $loc3$ (FIG. 2) is given by the mass flow of the substance at $loc1$ and considering any mass flow of the substance into the EC circuit 10 upstream of $loc3$.

[0074] The concentration of post-filter total calcium is dependent on the amount of the total calcium that is free for transport over the membrane 11a and the amount of protein-bound calcium that cannot pass the membrane 11a. When using RCA, a relatively large portion of free calcium will bind citrate, and citrate-calcium complexes will be lost through the membrane 11a. In one example, the extended model involves computing the clearance for different solutes in the dialyzer 11 as a function of the flow rates and the concentrations of the solute at the inlets of the dialyzer. The term "clearance" is well-known to the skilled person and is defined as the mass transfer rate for a solute divided by its plasma concentration or by the concentration gradient if the solute is present on both sides of the membrane 11a. In the present disclosure, no distinction is made between clearance and dialysance. The clearance depends on the flow rates of blood and dialysis fluid, the applied ultrafiltration rate (Q_{FIL}), and characteristics of the membrane 11a. There are established

equations for computing clearance for small uncharged water soluble substances, both under pure diffusive conditions and with significant convective transport across the membrane 11a. In one example, the extended model may be based on the principles disclosed in the article "Diffusive-convective mass transfer rates for solutes present on both sides of a dialyzer membrane" by Sternby et al, published in ASAIO J 51(3):246-251, 2005. The equations in the article are given for uncharged substances, and thus the mass transport rate is assumed to be a linear function of the inlet concentrations, since the driving forces for diffusion and convection are linear. For charged solutions, equations for clearance may also consider the electrical potential across the membrane. If required, such a membrane potential arises to maintain electro-neutrality. Since all of the charged solutes act together, a calculation of the transportation of one ion may, to be reasonably accurate, consider other relevant ions in the solution. Further, calculation of solute transportation may also consider complex binding between ions. When a complex transfers across the membrane 11a, its concentration will change on both sides of the membrane 11a and affect the equilibrium between the complex and its individual components. Since, these changes affect the concentration gradient and the transport rate for these components across the membrane 11a, equilibrium equations may be included in the calculation of the mass transfers. The calculation of mass transfer rates involves the mass transfer area coefficients of the various solutes, which are available in handbooks or may be estimated. In one example, the extended model considers complexes formed with albumin, which is a major component of blood and is known to bind a variety of charged solutes like sodium, calcium, magnesium and hydrogen ions. The extended model may also consider that each albumin molecule may bind a large number of these ions with different equilibrium constants and that this binding is pH dependent. In a further example, the extended model may consider complexes formed when calcium and magnesium bind to bicarbonate and citrate.

[0075] For the transport algorithm, the membrane 11a may be considered to be composed of a number of serial segments. For each membrane segment, the transport of each solute and each complex may be calculated separately, taking the membrane potential into account. With the given inlet concentration for each solute, the outlet concentrations for a membrane segment may be calculated from the transports. The total concentration of each compound may be calculated by summing the free concentration and the concentrations of all complexes where they appear. From the total concentration, a new distribution between free concentration and relevant complexes may be calculated. The recalculated concentration may be used as input to the next membrane segment. This calculation is done iteratively along the whole membrane 11a until a steady state situation is reached.

[0076] The skilled person understands that the extended model may be derived in many different ways and the foregoing is merely to be regarded as guiding principles. In any event, the extended model results in a non-linear system of equations, which may be numerically solved to render an extended function $f_{iCa_{ext}}$ that gives ionized calcium at any location in the EC circuit 10 as a function of modeled substances at this location.

[0077] In one example, the extended model is configured to handle 26 chemical reactions and, after adding equations for totals of involved substances including calcium and electro-neutrality, the extended model results in a non-linear system of 37 equations. The extended function $f_{iCa_{ext}}$ may be a function of variables such as totals of calcium, magnesium, sodium, chloride, potassium, bicarbonate, hydrogen phosphate, sulfate, citrate, acetate, lactate and albumin.

[0078] The extended model may also result in an equation for the total calcium at *loc2*, i.e. Ca_2 , e.g. by considering mass flow balance between *loc1* and *loc3*, and losses in the dialyzer 11 between *loc3* and *loc2*. In one example, such an equation is given by:

$$Ca_{PW2} = (Q_{PLASMA} - K_{Ca} \cdot F_{CAL} \cdot F_{DIL} \cdot Ca_{SYS}) \cdot \left(\frac{1}{Q_{PWI} - Q_{FIL}} \right)$$

where K_{Ca} is the clearance of calcium in the dialyzer 11, F_{CAL} may be approximated by a constant number (e.g. in range 0.8-1), and

$$Q_{PLASMA} = (1 - H) \cdot Q_B \cdot 60$$

$$F_{DIL} = \frac{Q_{PW}}{Q_{PWI}}$$

$$Q_{PWI} = Q_{PW} + Q_{PBP} + Q_{PRE}$$

$$Q_{PW} = (1 - H) \cdot f_{pw} \cdot Q_B \cdot 60$$

$$Q_{FIL} = Q_E - Q_D$$

[0079] Further, Ca_2 may be obtained from Ca_{PW2} by straight-forward conversion:

$$Ca_2 = Ca_{PW2} \cdot fpw_2$$

where

$$fpw_2 = 1 - \frac{Q_B \cdot 60 \cdot (1 - H)}{(1 - H_2) \cdot (60 \cdot Q_B + Q_{PBP} + Q_{PRE} - Q_{FIL}) \cdot (1 - fpw)}$$

$$H_2 = Q_B \cdot 60 \cdot \frac{H}{Q_B \cdot 60 + Q_{PBP} + Q_{PRE} - Q_{FIL}}$$

[0080] Thus, in this example, an equation for the total calcium at *loc2* may be given as a second function $Ca_2 = f_{0,2}(Ca_{SYS}, H, fpw, K_{Ca}, F_{CAL}, Q_B, Q_{PRE}, Q_E, Q_D, Q_{PBP})$.

[0081] The extended model may also result in an equation for the total citrate at *loc2*, i.e. CIT_2 , e.g. by considering mass flow balance between *loc1* and *loc3*, and losses in the dialyzer 11 between *loc3* and *loc2*. In one example, such an equation is given by:

$$CIT_{PW2} = (D_{CIT} \cdot Q_B \cdot 60) + (CIT_{SYS} \cdot Q_{PLASMA}) \cdot \left(1 - \frac{K_{CIT}}{Q_{PWI}}\right) \cdot \left(\frac{1}{Q_{PWI} - Q_{FIL}}\right)$$

[0082] In this example, citrate dose D_{CIT} is given in mmol/L and defined by the equation:

$$D_{CIT} = \frac{CIT_{PBP} \cdot Q_{PBP}}{Q_B \cdot 60}$$

where CIT_{PBP} is the citrate concentration in source 22.

[0083] It is understood that CIT_2 may be obtained from CIT_{PW2} by straight-forward conversion:

$$CIT_2 = CIT_{PW2} \cdot fpw_2$$

[0084] Thus, in this example, an equation for the total citrate at *loc2* may be given as a third function $CIT_2 = f_{0,3}(CIT_{SYS}, H, fpw, K_{CIT}, D_{CIT}, Q_B, Q_{PRE}, Q_E, Q_D, Q_{PBP})$.

[0085] As seen, $f_{0,3}$ depends on the total citrate in the patient's blood, CIT_{SYS} . In one embodiment, CIT_{SYS} may be set to a fixed value. However, it has been found that improved results may be achieved by instead modeling CIT_{SYS} as a function of treatment time. Such modeling may be performed in many different ways. One example is described in the article "Citrate Pharmacokinetics in Critically Ill Patients with Acute Kidney Injury", by Zheng et al., published in PLoS One Vol. 8,6 (2013). An equation for the systemic total citrate as a function of time may be given by:

$$CIT_{SYS} = CIT_0 \cdot e^{-(K_{CIT}/1000 + K_{BODY}) \cdot \left(\frac{t}{V_D}\right)} + (J_{CITLOAD} + G_{MET}) \cdot \left(\frac{1}{K_{CIT}/1000 + K_{BODY}}\right) \cdot \left(1 - e^{-(K_{CIT}/1000 + K_{BODY}) \cdot \left(\frac{t}{V_D}\right)}\right)$$

where CIT_0 is the level of systemic total citrate at the start of RCA and may be set to a predefined or measured value, and t is the time from start of RCA, and $J_{CITLOAD} = D_{CIT} \cdot Q_B \cdot 60 \cdot 10^{-3}$. This equation accounts for the rate of body metabolism of citrate (G_{MET}) and also accounts for the infusion of citrate into the EC circuit 10 and the loss (clearance) of total citrate in the dialyzer 11.

[0086] Although not shown herein, the model may be modified to account for an abnormal metabolic rate in the patient, e.g. by modifying the parameter G_{MET} .

[0087] Thus, in this example, an equation for the systemic total citrate may be given as a fourth function $CIT_{SYS} = f_{0,4}(CIT_0, V_D, K_{BODY}, G_{MET}, D_{CIT}, Q_B, K_{CIT}, t)$.

[0088] As understood from the foregoing, the extended model may also include one or more equations for calculation of the clearance of total citrate and total calcium in the dialyzer. Such equations are well-known in the art and the clearance for substance Y may be represented as a fifth function $K_Y = f_{0,5}(k_0 A_Y, \alpha_Y, Q_B, Q_D, Q_{FIL})$.

[0089] The extended model may also comprise an equation for conversion of systemic ionized calcium, iCa_{SYS} , to systemic total calcium, Ca_{SYS} . Such an equation may be derived by considering Ca_{SYS} as the sum of the different forms of calcium in plasma, e.g. iCa , $CaAlb$, $CaHCO_3$, $CaPO_4$, $CaCit$ and $CaCit_2$. The model may quantify each form by considering its chemical equilibrium. For example, $CaCit = iCa_{SYS} \cdot iCIT \cdot EQ_{CaCit}$, where $CaCit$ and $iCIT$ are the concentration of $CaCit$ and ionized citrate, respectively, and EQ_{CaCit} is the equilibrium association constant for $CaCit$. Further, the model may account for the fact that albumin has 12 binding sites that may be occupied by free calcium, and that the number of occupied binding sites (nCa_{REF}) is dependent on pH:

$$nCa_{REF} = 1.58 + 0.907 \cdot (pH - 7.4)$$

[0090] In one example, an equation for the systemic total calcium may be given by:

$$\begin{aligned} Ca_{SYS} = iCa_{SYS} \cdot \left(1 + 12 \cdot \frac{Alb}{(EQ_{Ca} + iCa_{SYS})} \right) &+ \frac{HCO_3}{1000} \cdot EQ_{CaHCO_3} \\ &+ \frac{HCO_3}{1000 \cdot 10^{\frac{pH}{EQ_{CaCO_3}}}} \\ &+ \frac{iP \cdot EQ_{CaPO_4}}{1000} + \frac{iCIT \cdot EQ_{CaCit}}{1000} + \frac{iCIT \cdot \frac{iCIT \cdot EQ_{CaCit_2}}{1000}}{1000} \end{aligned}$$

where EQ_{CaHCO_3} , EQ_{CaCO_3} , EQ_{CaPO_4} , EQ_{CaCit} , EQ_{CaCit_2} may be taken from handbooks, and EQ_{Ca} may be calculated as:

$$EQ_{Ca} = iCa_{REF} \cdot \left(\frac{12}{nCa_{REF}} - 1 \right)$$

with $iCa_{REF} = 1.25$ mmol/L.

[0091] Thus, in this example, an equation for the systemic total calcium may be given as a sixth function $Ca_{SYS} = f_{0,6}(iCa_{SYS}, Alb, HCO_3, pH, EQ_{CaX}, iCIT, iCa_{REF}, iP)$, where EQ_{CaX} represents the equilibrium association constants EQ_{Ca} , EQ_{CaHCO_3} , EQ_{CaCO_3} , EQ_{CaPO_4} , EQ_{CaCit} , EQ_{CaCit_2} .

[0092] Reverting now to FIG. 4, it is seen that the extended computation function $f_{iCa_{ext}}$ and the second to sixth computation functions $f_{0,2}$, $f_{0,3}$, $f_{0,4}$, $f_{0,5}$, $f_{0,6}$ are provided to block 401, in which a reduced model is determined to define the predefined algorithm for use in the RCA monitoring.

[0093] One reason for block 401 is that full solving of $f_{iCa_{ext}}$ requires significant computing capacity. In an attempt to reduce the complexity of $f_{iCa_{ext}}$, the inventors have made computer simulations which indicate that the extended function has a major dependence on the totals for calcium and citrate, and a smaller dependence on other variables. Therefore, to simplify computations, $f_{iCa_{ext}}$ may be linearized with respect to the variables of total calcium (Ca_x) and total citrate (CIT_x), where subscript x denotes an arbitrary location in the EC circuit 10:

$$\begin{aligned} f_{0,1}(Ca_x, CIT_x) = f_{iCa_{ext}}(Ca_{REF}, CIT_{REF}) &+ \frac{\delta f_{iCa_{ext}}}{\delta Ca_x}(Ca_{REF}, CIT_{REF}) \cdot (Ca_x - Ca_{REF}) + \\ &\frac{\delta f_{iCa_{ext}}}{\delta CIT_x}(Ca_{REF}, CIT_{REF}) \cdot (CIT_x - CIT_{REF}) \end{aligned}$$

[0094] The linearization is further illustrated in FIG. 5 which schematically depicts a three-dimensional space which is spanned by the dimensions iCa_x , Ca_x , and CIT_x , and where different evaluation points p_i are indicated by open circles. Each evaluation point p_i is given by a pair of coordinates in the Ca_x and CIT_x dimensions. Specifically, the extended

function $f_{iCa_{ext}}$ is evaluated at evaluation points p_i selected around and including a reference point p_{REF} , which is given by reference values for total calcium (Ca_{REF}) and total citrate (CIT_{REF}). The reference values are selected to be relevant at the post-dialyzer location, $loc2$, and may be nominal (desired) values at this location. As indicated in FIG. 5, the derivative of $f_{iCa_{ext}}$ in the Ca_x dimension ($\delta f_{iCa_{ext}}/\delta Ca_x$) and in the CIT_x dimension ($\delta f_{iCa_{ext}}/\delta CIT_x$) at the reference point p_{REF} may be estimated based on the evaluated values of $f_{iCa_{ext}}$ at a number of evaluation points p_i in the Ca_x dimension and the CIT_x dimension, respectively. The linearized function $f_{0,1}$ makes it possible to compute ionized calcium at $loc2$, i.e. iCa_2 , based on current values of total citrate, CIT_2 , and total calcium, Ca_2 , at $loc2$, represented by p_2 in FIG. 5. The linearization may also involve comparing the outputs of $f_{0,1}$ and $f_{iCa_{ext}}$ to verify that a sufficient agreement is achieved within a region of interest 500, i.e. for all relevant values of total calcium and total citrate at $loc2$.

[0095] The values of parameters included in the extended function, $f_{iCa_{ext}}$, other than the modeled parameters may be estimated based on experience and/or be taken from literature and handbooks and/or be obtained for a relevant population of patients. In the latter example, at least some of the parameter values may be obtained as an average of a respective machine setting or measured physiological parameter, e.g. for a specific clinic, group of clinics, etc. Thereby, the extended function may be tailored to a specific environment.

[0096] To summarize, and as indicated in block 401 in FIG. 4, the linearization may be seen to result in a linear function for calculating iCa based on Ca and CIT in $loc2$:

$$iCa_2 = f_{0,1}(Ca_2, CIT_2) = \beta_0 + \beta_1 \cdot (Ca_2 - Ca_{REF}) + \beta_2 \cdot (CIT_2 - CIT_{REF})$$

where β_0 , β_1 and β_2 are constants given by the linearization. In one example, iCa_2 is calculated in mmol/L and the parameters of $f_{0,1}$ are given by $\beta_0 = [0.32, 0.45]$, $\beta_1 = [0.29, 0.41]$, $\beta_2 = [-0.15, -0.05]$, $Ca_{REF} = [1.15, 1.55]$ and $CIT_{REF} = [2.00, 2.80]$, where the respective pair of brackets defines an interval which is inclusive of the start and end values.

[0097] FIG. 10 contains a summary overview of the functions $f_{0,1} - f_{0,6}$ as well additional functions described further below.

[0098] Block 401 may also involve defining one or more final functions to be used in the algorithmic computations by block 410. For example, as indicated in block 401, the computation functions $f_{0,1}$, $f_{0,2}$, $f_{0,3}$, $f_{0,5}$, $f_{0,6}$ may be combined into an aggregated computation function that directly outputs post-dialyzer ionized calcium, iCa_2 , based on measured values of systemic ionized calcium and systemic total citrate: $iCa_2 = f_1(iCa_{SYS}, CIT_{SYS})$. The use of an aggregated function is optional; post-dialyzer ionized calcium, iCa_2 may instead be computed by evaluating $f_{0,1}$, $f_{0,2}$, $f_{0,3}$, $f_{0,4}$, $f_{0,5}$, $f_{0,6}$ in suitable sequence based on measured values of iCa_{SYS} . Thus, any reference to f_1 in the following may imply the aggregated function or the sequence of functions $f_{0,1}$, $f_{0,2}$, $f_{0,3}$, $f_{0,5}$, $f_{0,6}$ or any composite functions formed therefrom.

[0099] Block 401 may also involve assigning one or more fixed generic values, which are presumed valid for the relevant systems 1, modalities and patients, to one more parameters that are used in the above-mentioned functions. Such parameter(s) may be constant and, e.g., include one or more of F_{CAL} , H , fpw , CIT_0 , G_{MET} , K_{BODY} , V_D , k_0A_Y , α_Y , Alb , HCO_3 , pH , EQ_{CaX} , $iCIT$, iCa_{REF} and iP . It is also conceivable that block 401 involves defining one or more approximation functions for estimating one or more parameters in dependence of a measurable property of the patient 100. Such approximation function(s) may, e.g., include one or more of: $G_{MET} = 0.0167 \cdot W$, $V_D = (29/72) \cdot W$ and $K_{BODY} = 7.79 \cdot W \cdot 60 \cdot 10^{-3}$, where W is the weight of the patient.

[0100] In the example of FIG. 4, block 401 also involves defining (e.g., based on $f_{0,6}$) a final function for computing systemic total calcium based on systemic ionized calcium: $Ca_{SYS} = f_2(iCa_{SYS})$, and defining (e.g., based on $f_{0,4}$) a final function for estimating systemic total citrate as a function of time: $CIT_{SYS} = f_3(t)$.

[0101] As shown in FIG. 4, block 401 provides a set of computation functions f_1 , f_2 , f_3 to the computation module 410, in which the set of functions f_1 , f_2 , f_3 forms the core of a predefined algorithm for computation of post-dialyzer ionized calcium, iCa_2 , and optionally further parameters. In the illustrated example, the predefined algorithm comprises the functions:

$$\begin{cases} iCa_2 = f_1(iCa_{SYS}, CIT_{SYS}) \\ Ca_{SYS} = f_2(iCa_{SYS}) \\ CIT_{SYS} = f_3(t) \\ R_{Ca} = Ca_{SYS}/iCa_{SYS} \end{cases}$$

where R_{Ca} is the calcium ratio which is conventionally used for evaluating citrate accumulation during RCA, as explained in the Background section. It should be noted that the dependence of the respective function on various parameters is not exhaustive. For example, as understood from the foregoing, the function f_1 depends on several additional parameters, such as flow rates, clearances, etc. Likewise, function f_2 several additional parameters, such as concentrations of albumin and bicarbonate in the patient's blood, pH of the patient's blood, etc.

[0102] The computation module 401 operates the predefined algorithm on current measurement data 402. In the illustrated example the measurement data 402 is a measured value of iCa_{SYS} , which is typically measured at $loc1$ in FIG. 2. The computation block 410 also operates on further input data, which includes one or more current values of machine settings (MS) 403 of the blood treatment system 1, and may also include one or more physiological parameters (PP) 404 of the patient 100, one or more system parameters (SP) 405 relating to the configuration of the system 1, and one or more chemical parameters (CP) 406. Examples of such parameters are given in the table of FIG. 6. As used herein, "machine settings" are current values of operation parameters for the blood treatment system 1, "physiological parameters" define the physiological state of the patient 100 or a group of representative patients, "system parameters" define the current structural configuration of the blood treatment system 1, and "chemical parameters" define chemical characteristics of blood.

[0103] Some of the parameters in FIG. 6 may be considered as constants. Generic values of such constants may be pre-stored in memory (cf. 42 in FIG. 1) for retrieval by the module 410. Alternatively, as explained above, generic values of one or more constants may instead be embedded in the set of functions f_1, f_2, f_3 .

[0104] The values of at least some of the parameters in FIG. 6 may be entered by the operator of the system 1 before start-up of a blood treatment session or, depending on implementation, may be calculated by the control device (40 in FIG. 1) before and/or during the blood treatment session. Such parameters may include one or more machine settings (MS), e.g. one or more of treatment time, total fluid to be removed from the patient, blood flow rate (Q_B), dialysis fluid flow rate (Q_D), effluent flow rate (Q_E), flow rate of replacement fluid upstream of dialyzer (Q_{PRE}), flow rate of replacement fluid downstream of dialyzer (Q_{POST}), ultrafiltration rate (Q_{FIL}), flow rate of citrate-containing fluid (Q_{PBP}), citrate dose (D_{CIT}), etc. It is also conceivable that block 410 obtains one or more machine settings from sensor(s) in the system 1, e.g. flow rate sensor(s), pump speed sensor(s), etc. It should be noted that one or more of the machine settings (MS) may be changed, by the operator or the control device, during the treatment session and that the computation block 410 may be configured to account for such changes by entering the changed parameter values into the predefined computation algorithm.

[0105] The operator may also enter current values of patient parameters (PP), such as hematocrit (H), albumin concentration (Alb), bicarbonate concentration (HCO_3), weight (W), blood pH (pH), etc. Concentration values and pH may be given by laboratory analysis of the patient's blood and may alternatively pre-stored in the memory (42 in FIG. 1) for subsequent retrieval.

[0106] With respect to the examples of system parameters (SP) in FIG. 6, it may be noted that the clearance parameters K_{Ca} , K_{CIT} may be included in input data in so far as they are fixed values rather than calculated by the function $f_{0.5}$. In addition to the parameter examples in FIG. 6, the operator may also indicate the type of fluid within one or more of the sources 13, 20, 21, 22, 23 (FIG. 2), so that the composition of the fluid is known to block 410. For example, the predefined algorithm may be configured to account for the concentration of calcium or citrate, if present in any of the fluids.

[0107] The system in FIG. 4 may implement the RCA monitoring 300 of FIG. 3. Thus, the computation module 410 may be configured to obtain the current measurement data 402, which represents a current measured value of systemic ionized calcium (iCa_{SYS}) in accordance with step 301. Module 410 may be further configured to compute and output one or more current computation values, including a current value of post-dialyzer ionized calcium (iCa_2), by operating the predefined algorithm on the measurement data 402 and the further input data 403-406. As indicated in FIG. 4, output data from the module 410 may additionally include one or more of a current value of systemic total calcium (Ca_{SYS}), a current value of systemic total citrate (CIT_{SYS}), a current value of the calcium ratio (R_{Ca}), and the current measured value of systemic ionized calcium (iCa_{SYS}).

[0108] The system in FIG. 4 further comprises a monitoring module 420, which is configured to receive the output data from the computation module 410 and perform one or more monitoring operations based thereon, e.g. in accordance with step 303 in FIG. 3. In the illustrated example, the monitoring module 420 comprises a decision support sub-module 421, a presentation sub-module 422 and a safety check module 423.

[0109] The decision support module 421 is configured to obtain a predefined and clinically proven protocol 407 for blood treatment combined with RCA. The protocol 407 may be tailored to the current blood treatment system 1, such as its modality and the compositions of the fluids, and may define the type of dialyzer(s) that may be used, allowable ranges of individual machine settings, etc. Further, the protocol 407 may define acceptable range(s) for the output data from the module 410, as well as corrective measures to be taken when the output data falls outside the acceptable range(s). Protocols for blood treatment combined with RCA are defined based on experience and extensive testing. There are many available treatment protocols, including universal protocols such as the so-called Kalmar protocol, e.g. described in the article "Regional Citrate Anticoagulation in Continuous Renal Replacement Therapies", by Daga-Ruiz et al, published in Int J Crit Care Emerg Med 2018, 4:054, or local protocols defined by or for a specific clinic or clinic provider. The decision support module 421 comprises logic which is configured to process the protocol 407 to define a set of rules that associates ranges of output values, such as one or more of iCa_2 , Ca_{SYS} , iCa_{SYS} , R_{Ca} and CIT_{SYS} with corrective measures to be taken. The logic is further configured to compare the output data from the module 410 with the set of rules and, based on the comparison, determine if and how any settings of the system 1 should be modified to

improve the performance of the RCA. Based thereon, the module 421 may output one or more operational recommendations 408 for presentation to the operator, e.g. on the display device 45. The recommendation(s) 408 may, e.g., indicate one or more machine settings to be changed and a desired direction or amount of change.

[0110] The presentation sub-module 422 is configured to format and provide the output data for presentation on a display device 45. For example, the output data may be presented to show current values and/or trends to the operator.

[0111] The safety check module 423 is configured to compare the output data to one or more operational limits, which may be predefined and stored in memory or given by the protocol 407, and to cause an alarm device 430 to generate an audible and/or visible alarm signal whenever a deviation between the output data and the operational limit(s) is detected. Concurrently, the safety check module 423 may cause the system 1 to enter a safe operational mode, which is configured to safeguard the patient's health.

[0112] It is also conceivable to combine the monitoring module 420 with a control module so that the system in FIG. 4 is also configured to automatically determine suitable changes to machine settings based on the output data, e.g. in view of the protocol 407, and modify one or more of control signals for the blood treatment system 1 accordingly (cf. signals S1-S7 in FIG. 1), possibly subject to confirmation by the operator through use of the input device 44.

[0113] FIG. 7 is a flow chart of a computation method that may be performed by the computation module 410 in FIG. 4, e.g. when implemented on the device 40 in FIG. 1. In steps 701-704, chemical parameters CP, physiological parameters PP, system parameters SP and machine settings MS are initialized, in which corresponding variables are instantiated and assigned a value. In the illustrated example, the values have been entered via the input device 44 and stored in the memory 42, from which the values are read in steps 701-704. As understood from the foregoing discussion, some values may be entered well ahead of blood treatment, e.g. during configuration of the device 40, while other values may be entered by the operator in preparation for a specific treatment session. In step 705, the clearances of calcium and citrate (K_{Ca} , K_{CIT}) are calculated, e.g. by use of function $f_{0,5}$ or any equivalent function. In a variant, these clearances are set equal and calculated for one of calcium and citrate. In yet another variant, fixed values of K_{Ca} , K_{CIT} are included among the system parameters. In step 706, the systemic total citrate CIT_{SYS} is set to CIT_0 . The computation method is now prepared for performing computations as part of the RCA monitoring during a blood treatment session.

[0114] After being notified that RCA has started (step 707), a counter of the treatment time (t) is set to zero in step 708. In step 709, the computation method waits until the treatment time equals a sampling time point (t_s). At this time, the method proceeds to step 710 which computes a predicted value of systemic total citrate at the sampling time point, by evaluating function f_3 at $t = t_s$. In step 711, a measured value of systemic ionized calcium iCa_{SYS} is obtained, either by user input via the input device 44, or from the blood analysis apparatus 50 over the connection 52 (FIG. 1). In step 712, a value of post-dialyzer ionized calcium iCa_2 is computed by operating the function f_1 on the measured iCa_{SYS} value and the predicted CIT_{SYS} value (given by step 710). In step 713, a current value of systemic total calcium Ca_{SYS} is computed by operating function f_2 on the measured iCa_{SYS} value. In step 714, the calcium ratio R_{Ca} is computed based on the current values of iCa_{SYS} and CIT_{SYS} . In step 715, the current values of iCa_{SYS} , iCa_2 , Ca_{SYS} , R_{Ca} and CIT_{SYS} are output, whereupon the method returns to step 709, to wait for the next sampling time point. In one embodiment, the sampling time points are predefined and, e.g., given by a data structure stored in the memory 42. Alternatively or additionally, the next sampling time point may be implied whenever a measured iCa_{SYS} value is obtained (cf. step 711).

[0115] FIG. 8A graphically depicts the sequence of calculations that may be performed during execution of the computation method in FIG. 7. Open circles represent measured values, filled circles represent computed values, and arrows indicate the values used in the respective calculation. The graph in FIG. 7A presumes that measurements are taken every hour for the first three hours and then every fourth hour. At each such measurement (sampling time point), a current value of CIT_{SYS} is projected and used, together with the measured value of iCa_{SYS} , for computing a current value of iCa_2 . The measured value of iCa_{SYS} is further used for computing a current value of Ca_{SYS} which is used, together with measured value of iCa_{SYS} , for computing a current value of R_{Ca} . In the illustrated example, it is presumed that the current value of CIT_{SYS} is projected based on the preceding value of CIT_{SYS} . In an alternative, using function f_3 , current values of CIT_{SYS} are projected based on the value of CIT_{SYS} at time $t = t_0$ (CIT_0).

[0116] As explained with reference to FIG. 3, steps 301-302 may alternatively obtain a measured value of systemic total calcium, Ca_{SYS} , and compute a current value of post-dialyzer ionized calcium, iCa_2 , based on the measured value of Ca_{SYS} . Such an embodiment may be implemented by modification of the system in FIG. 4, in which the measurement data 402 is Ca_{SYS} instead of iCa_{SYS} . The computation of a current value of iCa_2 based on a measured value of Ca_{SYS} may be implemented in different ways. A few non-limiting examples are given below.

[0117] In a first example, a seventh function $f_{0,7}$ is provided to generate iCa_{SYS} as a function of Ca_{SYS} , by straightforward re-arrangement of variables in function $f_{0,6}$:

$$iCa_{SYS} = f_{0,7}(Ca_{SYS}, Alb, HCO_3, pH, EQ_{CaX}, iCIT, iCa_{REF}, iP)$$

[0118] In the first example, with reference to FIG. 4, block 401 may be seen to involve defining, based on $f_{0,7}$, a final

function for computing systemic ionized calcium based on systemic total calcium: $iCa_{SYS} = f_4(Ca_{SYS})$ and providing the set of functions f_1, f_3, f_4 to the computation module 410. The computation method in FIG. 7 may be modified accordingly, by step 711 obtaining a measured value of Ca_{SYS} , step 712 computing a value of iCa_{SYS} by operating the function f_4 on the measured value of Ca_{SYS} , and step 713 computing a value of iCa_2 operating the function f_1 on the computed value of iCa_{SYS} and the predicted value of CIT_{SYS} (given by step 710). FIG. 8B graphically depicts the sequence of calculations that may be performed during execution of such a modified computation method.

[0119] In a second example, with reference to FIG. 4, block 401 may be seen to involve combining functions $f_{0,1}, f_{0,2}, f_{0,3}, f_{0,5}$ into a final function for computing post-dialyzer ionized calcium based on systemic total calcium and systemic total citrate: $iCa_2 = f_1^*(Ca_{SYS}, CIT_{SYS})$ and to provide the set of functions f_1^*, f_3, f_4 to the computation module 410.

[0120] In a third example, block 401 may be seen to involve a further linearization of function $f_{-iCa_{ext}}$ to derive a linear function $f_{0,7}^*$ for calculating systemic iCa based on systemic Ca and systemic CIT . The linearization may be performed as exemplified with reference to FIG. 5 but at a reference point $PREF_2$ given by reference values for total calcium (Ca_{REF_2}) and total citrate (CIT_{REF_2}) in the blood of the patient. Such a linear function may be given by:

$$iCa_{SYS} = f_{0,7}^*(Ca_{SYS}, CIT_{SYS}) \\ = \beta_{0_2} + \beta_{1_2} \cdot (Ca_{SYS} - Ca_{REF_2}) + \beta_{2_2} \cdot (CIT_{SYS} - CIT_{REF_2})$$

where β_{0_2}, β_{1_2} and β_{2_2} are constants given by the linearization. By analogy with function f_1 , functions $f_{0,2}, f_{0,3}, f_{0,4}, f_{0,5}, f_{0,7}^*$ may be seen to form a final function $iCa_{SYS} = f_4^*(Ca_{SYS}, CIT_{SYS})$. Thus, in the third example, block 401 may provide the set of functions f_1, f_3, f_4^* or f_1^*, f_3, f_4^* to the computation module 410.

[0121] The utility of the computation method in FIG. 7 has been evaluated based on measurement data obtained for a plurality of patients when subjected to blood treatment by CRRT machines (Prismaflex® from Baxter Corporation) equipped with ST150 sets and operated predominantly in modality CVVHDF. Values of post-dialyzer ionized calcium, iCa_2 , were computed based on measured values of systemic ionized calcium, iCa_{SYS} , and compared to measured values of post-dialyzer ionized calcium. The measured values were obtained by blood sampling and BGA analysis as described with reference to FIG. 1. FIG. 9A is a comparison of average computed iCa_2 values versus average measured iCa_2 values, where each data point in FIG. 9A represents time averages of computed and measured values, respectively, for a respective patient. FIG. 9B shows an example of the difference between individual computed and measured iCa_2 values during a treatment session. FIG. 9C is a graph of the average difference between computed and measured iCa_2 values for a plurality of patients. The average of the data points in FIG. 9C is 0.013 mmol/L with a standard deviation of 0.019 mmol/L. FIG. 9D is a graph of the standard deviation of the difference between computed and measured iCa_2 values for the plurality of patients in FIG. 9C. Considering that a standard BGA typically has an nominal accuracy of $\pm 7.5\%$ and that BGAs are not certified for measurements of ionized calcium in the range of 0.2-0.5 mmol/L or for blood samples with high concentration of citrate, the results in FIGS 9A-9D indicate that the computation method is useful for replacing measurements of post-dialyzer ionized calcium in systems for blood treatment that involves RCA.

[0122] While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, it is to be understood that the invention is not to be limited to the disclosed embodiments, but on the contrary, is defined by the appended claims.

[0123] Further, while operations are depicted in the drawings in a particular order, this should not be understood as requiring that such operations be performed in the particular order shown or in sequential order, or that all illustrated operations be performed, to achieve desirable results. In certain circumstances, multitasking and parallel processing may be advantageous. Moreover, the separation of various system components in the embodiments described above should not be understood as requiring such separation in all embodiments. Reverting to FIG. 4, block 400 may not only represent a preparatory step for defining the extended model, but may be an operative module which is configured to adapt the extended model based on measurement data M, as indicated by dashed lines in FIG. 4, where the measurement data M is obtained at considerably lower rate than the input data 402. The measurement data M may comprise measured amounts of one or more forms of calcium, total calcium, or total citrate in the blood of the patient and/or in the blood at any location in the EC circuit 10. In one example, the measurement data M may include measured Ca_{SYS} values, and block 400 may adjust the function $f_{0,6}$ by comparing the measured Ca_{SYS} values to computed Ca_{SYS} values, which are obtained by operating $f_{0,6}$ on measured iCa_{SYS} values (cf. input data 402). In another example, the measurement data M may include measured CIT_{SYS} values, and block 400 may adjust the function $f_{0,4}$ by comparing the measured CIT_{SYS} values to computed Ca_{SYS} values given by $f_{0,4}$ as a function of treatment time. In yet another example, the measurement data M may include measured iCa_2 values and measured Ca_2 values, and block 400 may adjust the extended function $f_{-iCa_{ext}}$ by comparing the measured iCa_2 values to computed iCa_2 values, which are obtained by operating $f_{-iCa_{ext}}$ on the measured Ca_2 values.

[0124] Correspondingly, as also indicated in FIG. 4, block 401 may be an operative module which is configured to adapt the reduced model based on measurement data M, e.g. by adjusting any one of functions $f_1, f_1^*, f_2, f_3, f_4, f_4^*$.

[0125] It may also be noted that the linear function $f_{0,1}$ need not be derived, in block 401, by linearization of an extended function given by theoretical modeling of the system 1 but may instead be derived by linear regression analysis of time-coordinated measurement values of iCa_2 , Ca_2 and CIT_2 . Correspondingly, the linear function $f_{0,7}$ may be derived by linear regression analysis of time-coordinated measurement values of iCa_{SYS} , Ca_{SYS} and CIT_{SYS} . In a further variant, the extended model includes a respective extended function for each relevant form of calcium in the blood, including ionized calcium and one or more of CaAlb, CaHCO₃, CaPO₄, CaCit and CaCit₂. Correspondingly, the reduced model may include a respective linear function for each relevant form, where the respective linear function is obtained by linearization of the respective extended function with respect to variables Ca and CIT (cf. FIG. 5). The reduced model may also include a function for computing the total calcium and total citrate at $loc3$ (FIG. 2), by considering mass flow balance between $loc1$ and $loc3$. The reduced model may further comprise one or more functions for computing the loss (clearance) of the respective form of calcium through the dialyzer membrane, as well as a function for predicting CIT_{SYS} in the patient (cf. f_3). Based on the linear functions, the computation module 410 may be configured to compute, based on a measured value of Ca_{SYS} , the amount of the respective form of calcium in the patient's blood. Further, the module 410 may be configured to compute the amount of the respective form of calcium at $loc3$, compute and remove the respective loss through the dialyzer membrane, and sum the remaining amounts of the different forms of calcium to obtain the total calcium at $loc2$, i.e. Ca_2 . The module 410 may also be configured to compute a current value of systemic total citrate (CIT_{SYS}), compute a corresponding amount of total citrate at $loc3$, compute and remove the loss of total citrate through the dialyzer membrane, to obtain the total citrate at $loc2$, i.e. CIT_2 . The module 410 may then be configured to operate the linear function for ionized calcium on Ca_2 and CIT_2 to obtain iCa_2 . If the measured value (402) instead represents iCa_{SYS} , the module 410 may be configured to operate the function f_2 on the measured iCa_{SYS} value to obtain a computed Ca_{SYS} value for use in the further computations.

[0126] The foregoing description is based on the assumption that the treatment protocol prescribes monitoring of ionized calcium downstream of the dialyzer, at $loc2$ in FIG. 2 (post-dialyzer ionized calcium). As mentioned in the Background section, the treatment protocol may alternatively, or additionally, prescribe that ionized calcium should be monitored upstream of the dialyzer, at $loc3$ in FIG. 2 (pre-dialyzer ionized calcium). As understood from the description of block 400 hereinabove (FIG. 4), the analysis for obtaining computation functions relevant to $loc3$ is a subset of the analysis for obtaining computation functions relevant to $loc2$. Thus, the foregoing teachings readily enable the skilled person to modify the predefined algorithm (used in computation block 410) to yield a computation value that represents ionized calcium, iCa_3 , in blood at $loc3$, e.g. based on total calcium Ca_3 and total citrate CIT_3 at $loc3$, as indicated by a dashed box in FIG. 2. For example, with reference to FIG. 10, $f_{0,1}$ may be modified to define a functional relation between iCa_3 and Ca_3 , CIT_3 ; $f_{0,2}$ may be modified to define a functional relation between Ca_3 and Ca_{SYS} ; and $f_{0,3}$ may be modified to define a functional relation between CIT_3 and CIT_{SYS} . FIG. 11 is a flow chart of an example method 300' for performance monitoring of RCA during a blood treatment session based on pre-dialyzer ionized calcium. Steps 301'-304' correspond to steps 301-304 in FIG. 3 and need not be described in further detail.

Nomenclature

[0127]

Alb : albumin concentration (mmol/L)
 HCO_3 : bicarbonate concentration (mmol/L)
 Ca_{REF} : total calcium concentration at linearization reference point for $loc2$ (mmol/L)
 Ca_{REF_2} : total calcium concentration at linearization reference point for $loc1$ (mmol/L)
 Ca_x : total calcium concentration at location x (mmol/L)
 Ca_{SYS} : total calcium concentration in blood of patient (mmol/L)
 Ca_2 : total calcium concentration in blood at $loc2$ (mmol/L)
 Ca_3 : total calcium concentration in blood at $loc3$ (mmol/L)
 Ca_{PW2} : total calcium concentration in plasma water at $loc2$ (mmol/L)
 CIT_{REF} : total citrate concentration at linearization reference point for $loc2$ (mmol/L)
 CIT_{REF_2} : total citrate concentration at linearization reference point for $loc1$ (mmol/L)
 CIT_x : total citrate concentration in blood at location x (mmol/L)
 CIT_2 : total citrate concentration in blood at $loc2$ (mmol/L)
 CIT_3 : total citrate concentration in blood at $loc3$ (mmol/L)
 CIT_{PBP} : citrate concentration in citrate-containing fluid (mmol/L)
 CIT_{PW2} : total citrate concentration in plasma water at $loc2$ (mmol/L)
 iCa_{SYS} : ionized calcium concentration in blood of patient (mmol/L)
 iCa_2 : ionized calcium concentration in blood at $loc2$ (mmol/L)
 iCa_3 : ionized calcium concentration in blood at $loc3$ (mmol/L)

$iCIT$: ionized citrate concentration in blood of patient (mmol/L)
 iP : ionized phosphate concentration in blood of patient (mmol/L)
 D_{CIT} : citrate dose (mmol/L of blood)
 EQ_{CaHCO_3} : equilibrium association constant for $CaHCO_3$ (L/mmol)
 EQ_{CaCO_3} : equilibrium association constant for $CaCO_3$ (L/mmol)
 EQ_{CaP} : equilibrium association constant for CaP (L/mmol)
 EQ_{CaCIT} : equilibrium association constant for $CaCit$ (L/mmol)
 EQ_{CaCIT_2} : equilibrium association constant for $CaCit_2$ (L²/mmol²)
 fwp : plasma water fraction
 F_{DIL} : dilution ratio for plasma water when reaching dialyzer
 F_{CAL} : fraction of patient plasma total calcium made available in plasma water for transfer through dialyzer membrane after citrate infusion.
 G_{MET} : metabolic generation rate of citrate in the body of the patient (mmol/h)
 H : hematocrit of patient blood as fraction of 1
 k_0A_Y : mass transfer area coefficient of dialyzer for substance Y (mL/h)
 K_{BODY} : plasma clearance of citrate in the body of the patient (L/h)
 K_Y : plasma clearance of substance Y in the dialyzer (L/h)
 K_{Ca} : plasma clearance of calcium in the dialyzer (L/h)
 K_{CIT} : plasma clearance of citrate in dialyzer (L/h)
 Q_B : blood flow rate from patient (mL/min)
 Q_D : flow rate of dialysis fluid (mL/h)
 Q_E : flow rate of effluent (mL/h)
 Q_{PW} : plasma water flow rate (mL/h)
 Q_{PWI} : plasma water flow rate at dialyzer inlet (mL/h)
 Q_{POST} : flow rate of replacement fluid downstream of dialyzer (mL/h)
 Q_{PRE} : flow rate of replacement fluid upstream of dialyzer (mL/h)
 Q_{PBP} : flow rate of citrate-containing fluid (mL/h)
 Q_{FIL} : ultrafiltration rate (mL/h)
 t : time from start of RCA (h)
 V_D : volume of citrate distribution (L)
 W : weight of patient (kg)
 α_Y : Donnan factor

Claims

1. A monitoring device for a blood treatment system (1) comprising an extracorporeal blood circuit (10) which comprises a blood withdrawal line (10a) and a blood return line (10b) for connection to a vascular system of subject (100) and a dialyzer (11) intermediate the blood withdrawal and blood return lines (10a, 10b), wherein the blood treatment system (1) is configured for regional citrate anticoagulation, RCA, by administration of citrate to the extracorporeal blood circuit (10) upstream of the dialyzer (11) during a treatment session, said monitoring device being configured to, at consecutive time steps during the treatment session:

obtain a current measurement value (402) of systemic ionized calcium (iCa_{SYS}) or systemic total calcium (Ca_{SYS}), operate a predefined algorithm on the current measurement value to generate a current computation value that represents ionized calcium (iCa_2 , iCa_3) in blood at a selected location ($loc2$, $loc3$) downstream or upstream of the dialyzer (11) in the extracorporeal blood circuit (10), and present and/or evaluate the current computation value for assessment of the regional citrate anticoagulation.

2. The monitoring device of claim 1, which is further configured to obtain input data (403-406) comprising current values of operation parameters (MS) of the blood treatment system (1), and optionally one or more of system configuration data (SP) for the blood treatment system (1), chemical parameter data (CP) for substances in the blood, and physiological parameter data (PP) for the subject (100), wherein the monitoring device is configured to operate the predefined algorithm on the input data (403-406) and the current measurement value to generate the current computation value.

3. The monitoring device of claim 1 or 2, wherein the predefined algorithm comprises a first function ($f_{0,1}$) configured to estimate the ionized calcium (iCa_2 , iCa_3) in the blood at the selected location ($loc2$, $loc3$) in the extracorporeal

blood circuit (10), said first function ($f_{0,1}$) being linearly dependent on total calcium (Ca_2 , Ca_3) at the selected location ($loc2$, $loc3$) and total citrate (CIT_2 , CIT_3) at the selected location ($loc2$, $loc3$).

4. The monitoring device of claim 3, wherein the first function ($f_{0,1}$) is obtained by linearization of a non-linear function with respect to each of total calcium (Ca_x) and total citrate (CIT_x), wherein the non-linear function is a solution to a system of equations representing chemical reactions of calcium in free form and bound to other substances in blood, including citrate, while assuming predefined amounts of other substances than calcium and citrate.
5. The monitoring device of claim 4, wherein the linearization is performed with respect to reference values (Ca_{REF} , CIT_{REF}) of total calcium and total citrate, said reference values (Ca_{REF} , CIT_{REF}) corresponding to expected values of total calcium and total citrate, respectively, at the selected location ($loc2$, $loc3$).
6. The monitoring device of any one of claims 3-5, wherein the predefined algorithm comprises a second function ($f_{0,2}$) configured to estimate the total calcium (Ca_2 , Ca_3) in the blood at the selected location ($loc2$, $loc3$).
7. The monitoring device of claim 6, wherein the selected location ($loc2$) is downstream of the dialyzer (11), and wherein the second function ($f_{0,2}$) depends on the systemic total calcium (Ca_{SYS}) and represents a mass balance of total calcium that enters the extracorporeal blood circuit (10) in the blood from the subject (100) and total calcium in the blood at an intermediate location ($loc3$) in the extracorporeal blood circuit (10) upstream of the dialyzer (11), while accounting for fluid infusion into the extracorporeal blood circuit (10) intermediate the subject (100) and the intermediate location ($loc3$), wherein the second function ($f_{0,2}$) further accounts for a loss of total calcium from the blood in the dialyzer (11).
8. The monitoring device of any one of claims 3-7, wherein the predefined algorithm comprises a third function ($f_{0,3}$) configured to estimate the total citrate (CIT_2 , CIT_3) in the blood at the selected location ($loc2$, $loc3$) in the extracorporeal blood circuit (10).
9. The monitoring device of claim 8, wherein the selected location ($loc2$) is downstream of the dialyzer (11), wherein the third function ($f_{0,3}$) depends on systemic total citrate (CIT_{SYS}) and represents a mass balance of total citrate that enters the extracorporeal blood circuit (10) in the blood from the subject (100) and total citrate at an intermediate location ($loc3$) in the extracorporeal blood circuit (10) upstream of the dialyzer (11), while accounting for fluid infusion into the extracorporeal blood circuit (10) intermediate the subject (100) and the intermediate location ($loc3$), wherein the third function ($f_{0,3}$) further accounts for a loss of total citrate from the blood in the dialyzer (11).
10. The monitoring device of any one of claims 3-9, wherein the predefined algorithm further comprises a fourth function ($f_{0,4}$) configured to estimate systemic total citrate (CIT_{SYS}) as a function of time from start of the regional citrate anticoagulation.
11. The monitoring device of claim 10, wherein the fourth function ($f_{0,4}$) represents a metabolic generation rate of citrate in the subject (100) and further accounts for the administration of citrate into the extracorporeal blood circuit (10) upstream of the dialyzer (11) and a loss of total citrate from the blood in the dialyzer (11).
12. The monitoring device of any one of claims 3-11, wherein the predefined algorithm further comprises at least one fifth function ($f_{0,5}$) configured to estimate a clearance (K_{CIT}) of total citrate and a clearance (K_{Ca}) of total calcium from the blood in the dialyzer (11), wherein the monitoring device is configured to compute a loss of total citrate and a loss of total calcium in the dialyzer (11) based on the clearance (K_{CIT}) of total citrate and the clearance (K_{Ca}) of total calcium, respectively.
13. The monitoring device of any one of claims 3-12, wherein the predefined algorithm comprises a sixth function ($f_{0,6}$) configured to estimate systemic total calcium (Ca_{SYS}) as a function of the systemic ionized calcium (iCa_{SYS}).
14. The monitoring device of any one of claims 3-13, wherein the predefined algorithm comprises a seventh function ($f_{0,7}$, $f_{0,7}^*$) configured to estimate the systemic ionized calcium (iCa_{SYS}) as a function of the systemic total calcium (Ca_{SYS}).
15. The monitoring device of any one of claims 1-13, wherein the current measurement value represents the systemic ionized calcium (iCa_{SYS}) in the blood of the subject (100), wherein the monitoring device is further configured to operate the predefined algorithm on the current measurement value to generate a further current computation value

representing the systemic total calcium (Ca_{SYS}).

- 5 **16.** The monitoring device of any one of claims 1-12 and 14, wherein the current measurement value represents the systemic total calcium (Ca_{SYS}), wherein the monitoring device is further configured to operate the predefined algorithm on the current measurement value to generate a further current computation value representing the systemic ionized calcium (iCa_{SYS}).
- 10 **17.** The monitoring device of any one of claims 1-14, wherein the monitoring device is further configured to operate the predefined algorithm to generate a further current computation value representing systemic total citrate (CIT_{SYS}).
- 15 **18.** The monitoring device of any one of claims 15-17, wherein the monitoring device is further configured to evaluate at least the further current computation value for assessment of accumulation of citrate in the subject (100).
- 20 **19.** The monitoring device of any preceding claim, which further comprises an interface (43b) for signal communication with a blood analysis apparatus (50), wherein the monitoring device is further configured to, at the respective consecutive time step, obtain the measurement value from a signal received over the interface (43b) from the blood analysis apparatus (50).
- 25 **20.** The monitoring device of any preceding claim, which is further configured to output the current computation value for presentation on a display device (45).
- 30 **21.** The monitoring device of any preceding claim, which is further configured to evaluate the current computation value for detection of an alarm situation, and cause an alarm to be generated when the alarm situation is detected.
- 35 **22.** The monitoring device of any preceding claim, which further comprises a decision support module (421), which is configured to evaluate the current computation value in relation to a clinically proven protocol (407) for the regional citrate anticoagulation, obtain a recommendation (408) for operation of the blood treatment system (1) based on the protocol (407), and output the recommendation (408) for presentation on a display device (45).
- 40 **23.** The monitoring device of any preceding claim, which further comprises an interface (43a) for signal communication with a set of pumping devices (12, 13b, 14b, 20b, 21b, 22b, 23) in the blood treatment system (1), wherein the monitoring device is further configured to generate one or more control signals (S1-S7) for the set of pumping devices (12, 13b, 14b, 20b, 21b, 22b, 23) as a function of the current computation value, and provide the one or more control signals (S1-S7) to the interface (43a).
- 45 **24.** The monitoring device of any preceding claim, which is further configured, during the treatment session, to obtain measurement data (M) representing at least one of calcium and citrate in the blood of the subject (100) and/or the extracorporeal blood circuit (10), and adjust the predefined algorithm based on the measurement data (M).
- 50 **25.** A blood treatment system comprising an extracorporeal blood circuit (10) for connection to a vascular system of a subject (100), said extracorporeal blood circuit (10) comprising a blood withdrawal line (10a) and a blood return line (10b) for connection to the vascular system, and a dialyzer (11) intermediate the blood withdrawal and blood return lines (10a, 10b), said blood treatment system further comprising a pumping device (12) for pumping blood from the subject (100) through the blood withdrawal line (10a), the dialyzer (11) and the blood return line (10b) back to the subject (100), said blood treatment system further comprising a sub-system (22, 22a, 22b) which is operable to perform regional citrate anticoagulation, RCA, in relation to the extracorporeal blood circuit (10) and the subject (100), and a monitoring device in accordance with any one of claims 1-24.
- 55 **26.** A method of monitoring a blood treatment system (1) comprising an extracorporeal blood circuit (10) which is configured for connection to a vascular system of a subject (100) and comprises a dialyzer (11), wherein the blood treatment system (1) is configured for regional citrate anticoagulation, RCA, by administration of citrate to the extracorporeal blood circuit (10) upstream of the dialyzer (11) during a treatment session, said method comprising, at consecutive time steps during the treatment session:

obtaining (301; 301') a current measurement value of systemic ionized calcium (iCa_{SYS}) or systemic total calcium (Ca_{SYS}),

operating (302; 302') a predefined algorithm on the current measurement value to generate a current computation value representing ionized calcium (iCa_2) in blood at a selected location ($loc2$, $loc3$) downstream or upstream

of the dialyzer (11) in the extracorporeal blood circuit (10), and presenting and/or evaluating (303; 303') the current computation value for assessment of the regional citrate anticoagulation.

27. A computer-readable medium comprising computer instructions which, when executed by a processor (41), cause the processor (41) to perform the method of claim 26.

Patentansprüche

1. Überwachungsvorrichtung für ein Blutbehandlungssystem (1), das einen extrakorporalen Blutkreislauf (10) umfasst, der eine Blutentnahmeleitung (10a) und eine Blutrückführleitung (10b) zur Verbindung mit einem Gefäßsystem eines Probanden (100) und einen Dialysator (11) zwischen der Blutentnahme- und der Blutrückführleitung (10a, 10b) umfasst, wobei das Blutbehandlungssystem (1) für regionale Citrat-Antikoagulation, RCA, durch Verabreichung von Citrat an den extrakorporalen Blutkreislauf (10) stromaufwärts des Dialysators (11) während einer Behandlungssitzung ausgelegt ist, wobei die Überwachungsvorrichtung in sukzessiven Zeitschritten während der Behandlungssitzung ausgelegt ist zum:

Erhalten eines aktuellen Messwerts (402) von systemisch ionisiertem Calcium (iCa_{SYS}) oder systemischem Gesamtcalcium (Ca_{SYS}),
Ausführen eines vordefinierten Algorithmus am aktuellen Messwert, um einen aktuellen Berechnungswert zu erzeugen, der ionisiertes Calcium (iCa_2 , iCa_3) in Blut an einer ausgewählten Stelle ($loc2$, $loc3$) stromabwärts oder stromaufwärts des Dialysators (11) im extrakorporalen Blutkreislauf (10) darstellt, und
Darstellen und/oder Evaluieren des aktuellen Berechnungswerts zur Beurteilung der regionalen Citrat-Antikoagulation.

2. Überwachungsvorrichtung nach Anspruch 1, die ferner zum Erhalten von Eingabedaten (403-406) ausgelegt ist, die aktuelle Werte von Betriebsparametern (MS) des Blutbehandlungssystems (1) und optional eines oder mehrere von Systemkonfigurationsdaten (SP) für das Blutbehandlungssystem (1), chemischen Parameterdaten (CP) für Substanzen im Blut und physiologischen Parameterdaten (PP) für den Probanden (100) umfassen, wobei die Überwachungsvorrichtung so ausgelegt ist, dass sie den vordefinierten Algorithmus an den Eingabedaten (403-406) und dem aktuellen Messwert ausführt, um den aktuellen Berechnungswert zu erzeugen.

3. Überwachungsvorrichtung nach Anspruch 1 oder 2, wobei der vordefinierte Algorithmus eine erste Funktion ($f_{0,1}$) umfasst, die zum Schätzen des ionisierten Calciums (iCa_2 , iCa_3) im Blut an der ausgewählten Stelle ($loc2$, $loc3$) im extrakorporalen Blutkreislauf (10) ausgelegt ist, wobei die erste Funktion ($f_{0,1}$) linear abhängig ist vom Gesamtcalcium (Ca_2 , Ca_3) an der ausgewählten Stelle ($loc2$, $loc3$) und dem Gesamtcitrat (CIT_2 , CIT_3) an der ausgewählten Stelle ($loc2$, $loc3$).

4. Überwachungsvorrichtung nach Anspruch 3, wobei die erste Funktion ($f_{0,1}$) durch Linearisierung einer nichtlinearen Funktion in Bezug auf jedes von Gesamtcalcium (Ca_x) und Gesamtcitrat (CIT_x) erhalten wird, wobei die nichtlineare Funktion eine Lösung für ein System von Gleichungen ist, das chemische Reaktionen von Calcium in freier Form und gebunden an andere Substanzen im Blut, einschließlich Citrat, darstellt, während vordefinierte Mengen von anderen Substanzen als Calcium und Citrat vorausgesetzt werden.

5. Überwachungsvorrichtung nach Anspruch 4, wobei die Linearisierung in Bezug auf Referenzwerte (Ca_{REF} , CIT_{REF}) von Gesamtcalcium und Gesamtcitrat durchgeführt wird, wobei die Referenzwerte (Ca_{REF} , CIT_{REF}) erwarteten Werten von Gesamtcalcium bzw. Gesamtcitrat an der ausgewählten Stelle ($loc2$, $loc3$) entsprechen.

6. Überwachungsvorrichtung nach einem der Ansprüche 3 bis 5, wobei der vordefinierte Algorithmus eine zweite Funktion ($f_{0,2}$) umfasst, die zum Schätzen des Gesamtcalciums (Ca_2 , Ca_3) im Blut an der ausgewählten Stelle ($loc2$, $loc3$) ausgelegt ist.

7. Überwachungsvorrichtung nach Anspruch 6, wobei die ausgewählte Stelle ($loc2$) stromabwärts des Dialysators (11) ist, und wobei die zweite Funktion ($f_{0,2}$) vom systemischen Gesamtcalcium (Ca_{SYS}) abhängt und eine Massenbilanz von Gesamtcalcium, das in den extrakorporalen Blutkreislauf (10) im Blut vom Probanden (100) eintritt, und Gesamtcalcium im Blut an einer ausgewählten Zwischenstelle ($loc3$) im extrakorporalen Blutkreislauf (10) stromaufwärts des Dialysators (11) darstellt, während Flüssigkeitsinfusion in den extrakorporalen Blutkreislauf (10) zwischen dem

Probanden (100) und der Zwischenstelle (*loc3*) berücksichtigt wird, wobei die zweite Funktion ($f_{0,2}$) ferner einen Verlust von Gesamtcalcium aus dem Blut im Dialysator (11) berücksichtigt.

- 5 8. Überwachungsvorrichtung nach einem der Ansprüche 3 bis 7, wobei der vordefinierte Algorithmus eine dritte Funktion ($f_{0,3}$) umfasst, die zum Schätzen des Gesamtcitrats (CIT_2 , CIT_3) im Blut an der ausgewählten Stelle (*loc2*, *loc3*) im extrakorporalen Blutkreislauf (10) ausgelegt ist.
- 10 9. Überwachungsvorrichtung nach Anspruch 8, wobei die ausgewählte Stelle (*loc2*) stromabwärts des Dialysators (11) ist, und wobei die dritte Funktion ($f_{0,3}$) von systemischem Gesamtcitrat (CIT_{SYS}) abhängt und eine Massenbilanz von Gesamtcitrat, das in den extrakorporalen Blutkreislauf (10) im Blut vom Probanden (100) eintritt, und Gesamtcitrat im Blut an einer ausgewählten Zwischenstelle (*loc3*) im extrakorporalen Blutkreislauf (10) stromaufwärts des Dialysators (11) darstellt, während Flüssigkeitsinfusion in den extrakorporalen Blutkreislauf (10) zwischen dem Probanden (100) und der Zwischenstelle (*loc3*) berücksichtigt wird, wobei die dritte Funktion ($f_{0,3}$) ferner einen Verlust von Gesamtcitrat aus dem Blut im Dialysator (11) berücksichtigt.
- 15 10. Überwachungsvorrichtung nach einem der Ansprüche 3 bis 9, wobei der vordefinierte Algorithmus ferner eine vierte Funktion ($f_{0,4}$) umfasst, die zum Schätzen von systemischem Gesamtcitrat (CIT_{SYS}) als eine Funktion von Zeit ab Beginn der regionalen Citrat-Antikoagulation ausgelegt ist.
- 20 11. Überwachungsvorrichtung nach Anspruch 10, wobei die vierte Funktion ($f_{0,4}$) eine metabolische Erzeugungsrate von Citrat im Probanden (100) darstellt und ferner die Verabreichung von Citrat in den extrakorporalen Blutkreislauf (10) stromaufwärts des Dialysators (11) und einen Verlust von Gesamtcitrat aus dem Blut im Dialysator (11) berücksichtigt.
- 25 12. Überwachungsvorrichtung nach einem der Ansprüche 3 bis 11, wobei der vordefinierte Algorithmus ferner mindestens eine fünfte Funktion ($f_{0,5}$) umfasst, die zum Schätzen einer Clearance (K_{CIT}) von Gesamtcitrat und einer Clearance (K_{Ca}) von Gesamtcalcium aus dem Blut im Dialysator (11) ausgelegt ist, wobei die Überwachungsvorrichtung zum Berechnen eines Verlusts von Gesamtcitrat und eines Verlusts von Gesamtcalcium im Dialysator (11) basierend auf der Clearance (K_{CIT}) von Gesamtcitrat bzw. der Clearance (K_{Ca}) von Gesamtcalcium ausgelegt ist.
- 30 13. Überwachungsvorrichtung nach einem der Ansprüche 3 bis 12, wobei der vordefinierte Algorithmus eine sechste Funktion ($f_{0,6}$) umfasst, die zum Schätzen von systemischem Gesamtcalcium (Ca_{SYS}) als eine Funktion des systemisch ionisierten Calciums (iCa_{SYS}) ausgelegt ist.
- 35 14. Überwachungsvorrichtung nach einem der Ansprüche 3 bis 13, wobei der vordefinierte Algorithmus eine siebte Funktion ($f_{0,7}$, $f_{0,7}^*$) umfasst, die zum Schätzen des systemisch ionisierten Calciums (iCa_{SYS}) als eine Funktion des systemischen Gesamtcalciums (Ca_{SYS}) ausgelegt ist.
- 40 15. Überwachungsvorrichtung nach einem der Ansprüche 1 bis 3, wobei der aktuelle Messwert das systemisch ionisierte Calcium (iCa_{SYS}) im Blut des Probanden (100) darstellt, wobei die Überwachungsvorrichtung ferner so ausgelegt ist, dass sie den vordefinierten Algorithmus am aktuellen Messwert ausführt, um einen weiteren aktuellen Berechnungswert zu erzeugen, der das systemische Gesamtcalcium (Ca_{SYS}) darstellt.
- 45 16. Überwachungsvorrichtung nach einem der Ansprüche 1 bis 12 und 14, wobei der aktuelle Messwert das systemische Gesamtcalcium (Ca_{SYS}) darstellt, wobei die Überwachungsvorrichtung ferner so ausgelegt ist, dass sie den vordefinierten Algorithmus am aktuellen Messwert ausführt, um einen weiteren aktuellen Berechnungswert zu erzeugen, der das systemisch ionisierte Calcium (iCa_{SYS}) darstellt.
- 50 17. Überwachungsvorrichtung nach einem der Ansprüche 1 bis 14, wobei die Überwachungsvorrichtung ferner so ausgelegt ist, dass sie den vordefinierten Algorithmus ausführt, um einen weiteren aktuellen Berechnungswert zu erzeugen, der das systemische Gesamtcitrat (CIT_{SYS}) darstellt.
- 55 18. Überwachungsvorrichtung nach einem der Ansprüche 15 bis 17, wobei die Überwachungsvorrichtung ferner zum Evaluieren zumindest des weiteren aktuellen Berechnungswerts zur Beurteilung der Akkumulation von Citrat im Probanden (100) ausgelegt ist.
19. Überwachungsvorrichtung nach einem der vorhergehenden Ansprüche, die ferner eine Schnittstelle (43b) zur Signalkommunikation mit einem Blutanalysegerät (50) umfasst, wobei die Überwachungsvorrichtung ferner so ausge-

legt ist, dass sie den Messwert im jeweiligen sukzessiven Zeitschritt aus einem Signal erhält, das über die Schnittstelle (43b) vom Blutanalysegerät (50) empfangen wird.

20. Überwachungsvorrichtung nach einem der vorhergehenden Ansprüche, die ferner zum Ausgeben des aktuellen Berechnungswerts zur Darstellung auf einer Anzeigevorrichtung (45) ausgelegt ist.

21. Überwachungsvorrichtung nach einem der vorhergehenden Ansprüche, die ferner so ausgelegt ist, dass sie den aktuellen Berechnungswert zur Erkennung einer Alarmsituation evaluiert und bewirkt, dass ein Alarm ausgelöst wird, wenn die Alarmsituation erkannt wird.

22. Überwachungsvorrichtung nach einem der vorhergehenden Ansprüche, die ferner ein Entscheidungsunterstützungsmodul (421) umfasst, das so ausgelegt ist, dass es den aktuellen Berechnungswert in Bezug auf ein klinisch erprobtes Protokoll (407) für die regionale Citrat-Antikoagulation evaluiert, eine Empfehlung (408) für den Betrieb des Blutbehandlungssystems (1) basierend auf dem Protokoll (407) erhält und die Empfehlung (408) zur Darstellung auf einer Anzeigevorrichtung (45) ausgibt.

23. Überwachungsvorrichtung nach einem der vorhergehenden Ansprüche, die ferner eine Schnittstelle (43a) zur Signalkommunikation mit einem Satz von Pumpvorrichtungen (12, 13b, 14b, 20b, 21b, 22b, 23) im Blutbehandlungssystem (1) umfasst, wobei die Überwachungsvorrichtung ferner so ausgelegt ist, dass sie ein oder mehrere Steuersignale (S1-S7) für den Satz von Pumpvorrichtungen (12, 13b, 14b, 20b, 21b, 22b, 23) als eine Funktion des aktuellen Berechnungswerts erzeugt und das eine oder die mehreren Steuersignale (S1-S7) für die Schnittstelle (43a) bereitstellt.

24. Überwachungsvorrichtung nach einem der vorhergehenden Ansprüche, die ferner so ausgelegt ist, dass sie während der Behandlungssitzung Messdaten (M) erhält, die mindestens eines von Calcium und Citrat im Blut des Probanden (100) und/oder dem extrakorporalen Blutkreislauf (10) darstellen, und den vordefinierten Algorithmus basierend auf den Messdaten (M) anpasst.

25. Blutbehandlungssystem, umfassend einen extrakorporalen Blutkreislauf (10) zur Verbindung mit einem Gefäßsystem eines Probanden (100), wobei der extrakorporale Blutkreislauf (10) eine Blutentnahmeleitung (10a) und eine Blutrückführleitung (10b) zur Verbindung mit dem Gefäßsystem und einen Dialysator (11) zwischen der Blutentnahme- und der Blutrückführleitung (10a, 10b) umfasst, wobei das Blutbehandlungssystem ferner eine Pumpvorrichtung (12) zum Pumpen von Blut vom Probanden (100) durch die Blutentnahmeleitung (10a), den Dialysator (11) und die Blutrückführleitung (10b) zurück zum Probanden (100) umfasst, wobei das Blutbehandlungssystem ferner ein Subsystem (22, 22a, 22b), das regionale Citrat-Antikoagulation, RCA, in Bezug auf den extrakorporalen Blutkreislauf (10) und den Probanden (100) durchführt, und eine Überwachungsvorrichtung nach einem der Ansprüche 1 bis 24 umfasst.

26. Verfahren zur Überwachung eines Blutbehandlungssystems (1), das einen extrakorporalen Blutkreislauf (10) umfasst, der zur Verbindung mit einem Gefäßsystem eines Probanden (100) ausgelegt ist und einen Dialysator (11) umfasst, wobei das Blutbehandlungssystem (1) für regionale Citrat-Antikoagulation, RCA, durch Verabreichung von Citrat an den extrakorporalen Blutkreislauf (10) stromaufwärts des Dialysators (11) während einer Behandlungssitzung ausgelegt ist, wobei das Verfahren in sukzessiven Zeitschritten während der Behandlungssitzung umfasst:

Erhalten (301; 301') eines aktuellen Messwerts von systemisch ionisiertem Calcium (iCa_{SYS}) oder systemischem Gesamtcalcium (Ca_{SYS}),

Ausführen (302; 302') eines vordefinierten Algorithmus am aktuellen Messwert, um einen aktuellen Berechnungswert zu erzeugen, der ionisiertes Calcium (iCa_2) in Blut an einer ausgewählten Stelle ($loc2$, $loc3$) stromabwärts oder stromaufwärts des Dialysators (11) im extrakorporalen Blutkreislauf (10) darstellt, und

Darstellen und/oder Evaluieren (303; 303') des aktuellen Berechnungswerts zur Beurteilung der regionalen Citrat-Antikoagulation.

27. Computerlesbares Medium, umfassend Computeranweisungen, die bei Ausführung durch einen Prozessor (41) den Prozessor (41) zum Durchführen des Verfahrens nach Anspruch 26 veranlassen.

Revendications

1. Dispositif de surveillance pour un système de traitement du sang (1) comprenant un circuit sanguin extracorporel (10) qui comprend une ligne de prélèvement de sang (10a) et une ligne de retour de sang (10b) pour la connexion à un système vasculaire d'un sujet (100) et un dialyseur (11) entre les lignes de prélèvement de sang et de retour de sang (10a, 10b), où le système de traitement du sang (1) est configuré pour une anticoagulation régionale au citrate, RCA, par administration de citrate au circuit sanguin extracorporel (10) en amont du dialyseur (11) pendant une session de traitement, ledit dispositif de surveillance étant configuré pour, à des étapes temporelles consécutives pendant la session de traitement :
 - obtenir une valeur de mesure courante (402) du calcium ionisé systémique (iCa_{SYS}) ou du calcium total systémique (Ca_{SYS}) ,
 - faire fonctionner un algorithme prédéfini sur la valeur de mesure courante pour générer une valeur de calcul courante qui représente le calcium ionisé (iCa_2 , iCa_3) dans le sang à un emplacement sélectionné ($loc2$, $loc3$) en aval ou en amont du dialyseur (11) dans le circuit sanguin extracorporel (10), et
 - présenter et/ou évaluer la valeur de calcul courante pour l'évaluation de l'anticoagulation régionale au citrate.
2. Dispositif de surveillance selon la revendication 1, qui est en outre configuré pour obtenir des données d'entrée (403-406) comprenant des valeurs courantes de paramètres de fonctionnement (MS) du système de traitement du sang (1) et, éventuellement, une ou plusieurs données de configuration de système (SP) pour le système de traitement du sang (1), des données de paramètres chimiques (CP) pour des substances dans le sang, et des données de paramètres physiologiques (PP) pour le sujet (100), où le dispositif de surveillance est configuré pour faire fonctionner l'algorithme prédéfini sur les données d'entrée (403-406) et la valeur de mesure courante pour générer la valeur de calcul courante.
3. Dispositif de surveillance selon la revendication 1 ou la revendication 2, dans lequel l'algorithme prédéfini comprend une première fonction ($f_{0,1}$) configurée pour estimer le calcium ionisé (iCa_2 , iCa_3) dans le sang à l'emplacement sélectionné ($loc2$, $loc3$) dans le circuit sanguin extracorporel (10), ladite première fonction ($f_{0,1}$) dépendant linéairement du calcium total (Ca_2 , Ca_3) à l'emplacement sélectionné ($loc2$, $loc3$) et du citrate total (CIT_2 , CIT_3) à l'emplacement sélectionné ($loc2$, $loc3$).
4. Dispositif de surveillance selon la revendication 3, dans lequel la première fonction ($f_{0,1}$) est obtenue par linéarisation d'une fonction non linéaire par rapport à chacun du calcium total (Ca_x) et du citrate total (CIT_x), où la fonction non linéaire est une solution à un système d'équations représentant les réactions chimiques du calcium sous forme libre et lié à d'autres substances dans le sang, y compris le citrate, tout en supposant des quantités prédéfinies de substances autres que le calcium et le citrate.
5. Dispositif de surveillance selon la revendication 4, dans lequel la linéarisation est effectuée par rapport à des valeurs de référence (Ca_{REF} , CIT_{REF}) du calcium total et du citrate total, lesdites valeurs de référence (Ca_{REF} , CIT_{REF}) correspondant aux valeurs attendues du calcium total et du citrate total, respectivement, à l'emplacement sélectionné ($loc2$, $loc3$).
6. Dispositif de surveillance selon l'une quelconque des revendications 3 à 5, dans lequel l'algorithme prédéfini comprend une deuxième fonction ($f_{0,2}$) configurée pour estimer le calcium total (Ca_2 , Ca_3) dans le sang à l'emplacement sélectionné ($loc2$, $loc3$).
7. Dispositif de surveillance selon la revendication 6, dans lequel l'emplacement sélectionné ($loc2$) est en aval du dialyseur (11), et dans lequel la deuxième fonction ($f_{0,2}$) dépend du calcium total systémique (Ca_{SYS}) et représente un équilibre de masse du calcium total qui entre dans le circuit sanguin extracorporel (10) dans le sang du sujet (100) et du calcium total dans le sang à un emplacement intermédiaire ($loc3$) dans le circuit sanguin extracorporel (10) en amont du dialyseur (11), tout en tenant compte de l'infusion de fluide dans le circuit sanguin extracorporel (10) entre le sujet (100) et l'emplacement intermédiaire ($loc3$), où la deuxième fonction ($f_{0,2}$) tient en outre compte d'une perte de calcium total du sang dans le dialyseur (11).
8. Dispositif de surveillance selon l'une quelconque des revendications 3 à 7, dans lequel l'algorithme prédéfini comprend une troisième fonction ($f_{0,3}$) configurée pour estimer le citrate total (CIT_2 , CIT_3) dans le sang à l'emplacement sélectionné ($loc2$, $loc3$) dans le circuit sanguin extracorporel (10).

9. Dispositif de surveillance selon la revendication 8, dans lequel l'emplacement sélectionné (loc2) est en aval du dialyseur (11), où la troisième fonction ($f_{0,3}$) dépend du citrate total systémique (CIT_{SYS}) et représente un équilibre de masse du citrate total qui entre dans le circuit sanguin extracorporel (10) dans le sang du sujet (100) et du citrate total à un emplacement intermédiaire (loc3) dans le circuit sanguin extracorporel (10) en amont du dialyseur (11), tout en tenant compte de l'infusion de fluide dans le circuit sanguin extracorporel (10) entre le sujet (100) et l'emplacement intermédiaire (loc3), où la troisième fonction ($f_{0,3}$) tient en outre compte d'une perte de citrate total du sang dans le dialyseur (11). 5
10. Dispositif de surveillance selon l'une quelconque des revendications 3 à 9, dans lequel l'algorithme prédéfini comprend en outre une quatrième fonction ($f_{0,4}$) configurée pour estimer le citrate total systémique (CIT_{SYS}) en fonction du temps depuis le début de l'anticoagulation régionale au citrate. 10
11. Dispositif de surveillance selon la revendication 10, dans lequel la quatrième fonction (44) représente un taux de génération métabolique de citrate chez le sujet (100) et tient en outre compte de l'administration de citrate dans le circuit sanguin extracorporel (10) en amont du dialyseur (11) et d'une perte de citrate total du sang dans le dialyseur (11). 15
12. Dispositif de surveillance selon l'une quelconque des revendications 3 à 11, dans lequel l'algorithme prédéfini comprend en outre au moins une cinquième fonction ($f_{0,5}$) configurée pour estimer une clairance (K_{GIT}) du citrate total et une clairance (K_{Ca}) du calcium total à partir du sang dans le dialyseur (11), où le dispositif de surveillance est configuré pour calculer une perte de citrate total et une perte de calcium total dans le dialyseur (11) sur la base de la clairance (K_{GIT}) du citrate total et de la clairance (K_{Ca}) du calcium total, respectivement. 20
13. Dispositif de surveillance selon l'une quelconque des revendications 3 à 12, dans lequel l'algorithme prédéfini comprend une sixième fonction ($f_{0,6}$) configurée pour estimer le calcium total systémique (Ca_{SYS}) en fonction du calcium ionisé systémique (iCa_{SYS}). 25
14. Dispositif de surveillance selon l'une quelconque des revendications 3 à 13, dans lequel l'algorithme prédéfini comprend une septième fonction ($f_{0,7}, f_{0,7}^*$) configurée pour estimer le calcium ionisé systémique (iCa_{SYS}) en fonction du calcium total systémique (Ca_{SYS}). 30
15. Dispositif de surveillance selon l'une quelconque des revendications 1 à 13, dans lequel la valeur de mesure courante représente le calcium ionisé systémique (iCa_{SYS}) dans le sang du sujet (100), où le dispositif de surveillance est en outre configuré pour faire fonctionner l'algorithme prédéfini sur la valeur de mesure courante pour générer une autre valeur de calcul courante représentant le calcium total systémique (Ca_{SYS}). 35
16. Dispositif de surveillance selon l'une quelconque des revendications 1 à 12 et 14, dans lequel la valeur de mesure courante représente le calcium total systémique (Ca_{SYS}), où le dispositif de surveillance est en outre configuré pour faire fonctionner l'algorithme prédéfini sur la valeur de mesure courante pour générer une autre valeur de calcul courante représentant le calcium ionisé systémique (iCa_{SYS}). 40
17. Dispositif de surveillance selon l'une quelconque des revendications 1 à 14, dans lequel le dispositif de surveillance est en outre configuré pour faire fonctionner l'algorithme prédéfini pour générer une autre valeur de calcul courante représentant le citrate total systémique (CIT_{SYS}). 45
18. Dispositif de surveillance selon l'une quelconque des revendications 15 à 17, dans lequel le dispositif de surveillance est en outre configuré pour évaluer au moins l'autre valeur de calcul courante pour évaluer l'accumulation de citrate chez le sujet (100).
19. Dispositif de surveillance selon l'une quelconque des revendications précédentes, lequel comprend en outre une interface (43b) pour la communication de signaux avec un appareil d'analyse du sang (50), où le dispositif de surveillance est en outre configuré pour, à l'étape temporelle consécutive respective, obtenir la valeur de mesure à partir d'un signal reçu sur l'interface (43b) depuis l'appareil d'analyse de sang (50). 50
20. Dispositif de surveillance selon l'une quelconque des revendications précédentes, lequel est en outre configuré pour délivrer en sortie la valeur de calcul courante pour la présenter sur un dispositif d'affichage (45). 55
21. Dispositif de surveillance selon l'une quelconque des revendications précédentes, lequel est en outre configuré

pour évaluer la valeur de calcul courante pour la détection d'une situation d'alarme, et provoquer la génération d'une alarme lorsque la situation d'alarme est détectée.

22. Dispositif de surveillance selon l'une quelconque des revendications précédentes, lequel comprend en outre un module d'aide à la décision (421), lequel est configuré pour évaluer la valeur de calcul courante par rapport à un protocole cliniquement prouvé (407) pour l'anticoagulation régionale au citrate, obtenir une recommandation (408) pour le fonctionnement du système de traitement du sang (1) sur la base du protocole (407), et délivrer en sortie la recommandation (408) pour la présenter sur un dispositif d'affichage (45).

23. Dispositif de surveillance selon l'une quelconque des revendications précédentes, lequel comprend en outre une interface (43a) pour la communication de signaux avec un ensemble de dispositifs de pompage (12, 13b, 14b, 20b, 21b, 22b, 23) dans le système de traitement du sang (1), où le dispositif de surveillance est en outre configuré pour générer un ou plusieurs signaux de commande (S1-S7) pour l'ensemble de dispositifs de pompage (12, 13b, 14b, 20b, 21b, 22b, 23) en fonction de la valeur de calcul courante, et fournir les un ou plusieurs signaux de commande (S1-S7) à l'interface (43a).

24. Dispositif de surveillance selon l'une quelconque des revendications précédentes, lequel est en outre configuré, pendant la session de traitement, pour obtenir des données de mesure (M) représentant au moins l'un du calcium et du citrate dans le sang du sujet (100) et/ou le circuit sanguin extracorporel (10), et ajuster l'algorithme prédéfini sur la base des données de mesure (M).

25. Système de traitement du sang comprenant un circuit sanguin extracorporel (10) destiné à être connecté au système vasculaire d'un sujet (100), ledit circuit sanguin extracorporel (10) comprenant une ligne de prélèvement de sang (10a) et une ligne de retour de sang (10b) destinées à être connectées au système vasculaire, et un dialyseur (11) situé entre les lignes de prélèvement de sang et de retour de sang (10a, 10b), ledit système de traitement du sang comprenant en outre un dispositif de pompage (12) pour pomper le sang du sujet (100) à travers la ligne de prélèvement du sang (10a), le dialyseur (11) et la ligne de retour du sang (10b), et le renvoyer au sujet (100), ledit système de traitement du sang comprenant en outre un sous-système (22, 22a, 22b) qui est utilisable pour procéder à une anticoagulation régionale au citrate, RCA, en relation avec le circuit sanguin extracorporel (10) et le sujet (100), et un dispositif de surveillance selon l'une quelconque des revendications 1 à 24.

26. Procédé de surveillance d'un système de traitement du sang (1) comprenant un circuit sanguin extracorporel (10) qui est configuré pour être connecté au système vasculaire d'un sujet (100) et qui comprend un dialyseur (11), où le système de traitement du sang (1) est configuré pour une anticoagulation régionale au citrate, RCA, par administration de citrate au circuit sanguin extracorporel (10) en amont du dialyseur (11) pendant une session de traitement, ledit procédé comprenant, à des étapes temporelles consécutives pendant la session de traitement, les étapes suivantes :

obtenir (301 ; 301') une valeur de mesure courante (402) du calcium ionisé systémique (iCa_{SYS}) ou du calcium total systémique (Ca_{SYS}),
faire fonctionner (302 ; 302') un algorithme prédéfini sur la valeur de mesure courante pour générer une valeur de calcul courante qui représente le calcium ionisé (iCa_2) dans le sang à un emplacement sélectionné (loc_2 , loc_3) en aval ou en amont du dialyseur (11) dans le circuit sanguin extracorporel (10), et
présenter et/ou évaluer (303 ; 303') la valeur de calcul courante pour l'évaluation de l'anticoagulation régionale au citrate.

27. Support lisible par ordinateur comprenant des instructions informatiques qui, lorsqu'elles sont exécutées par un processeur (41), amènent le processeur (41) à exécuter le procédé de la revendication 26.

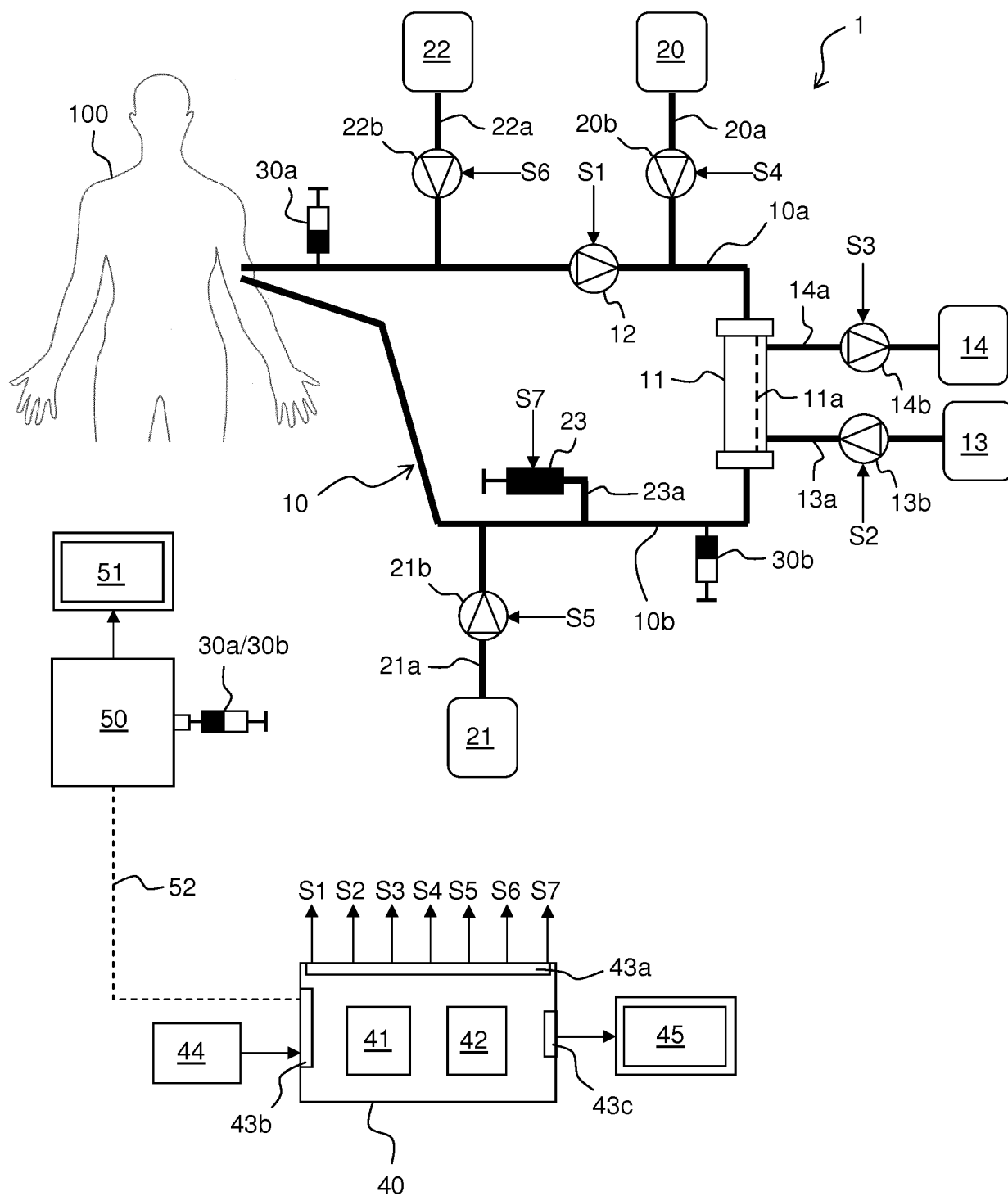


FIG. 1

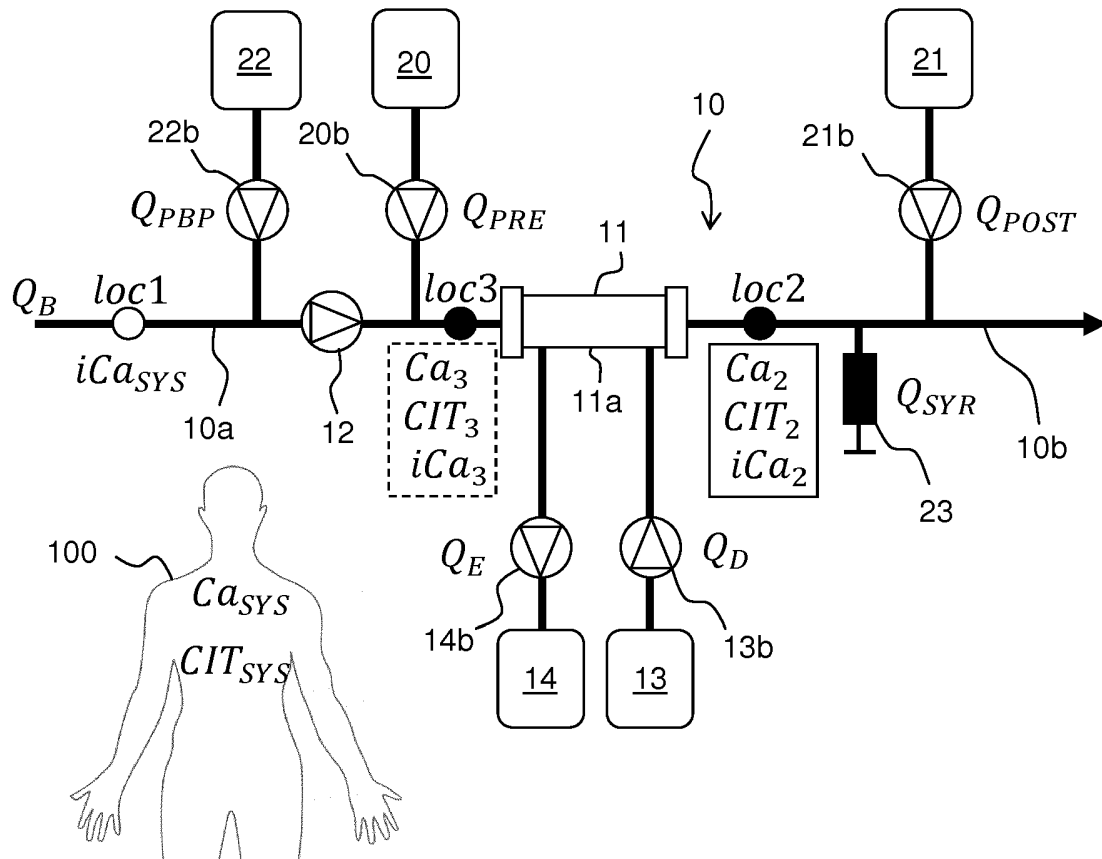


FIG. 2

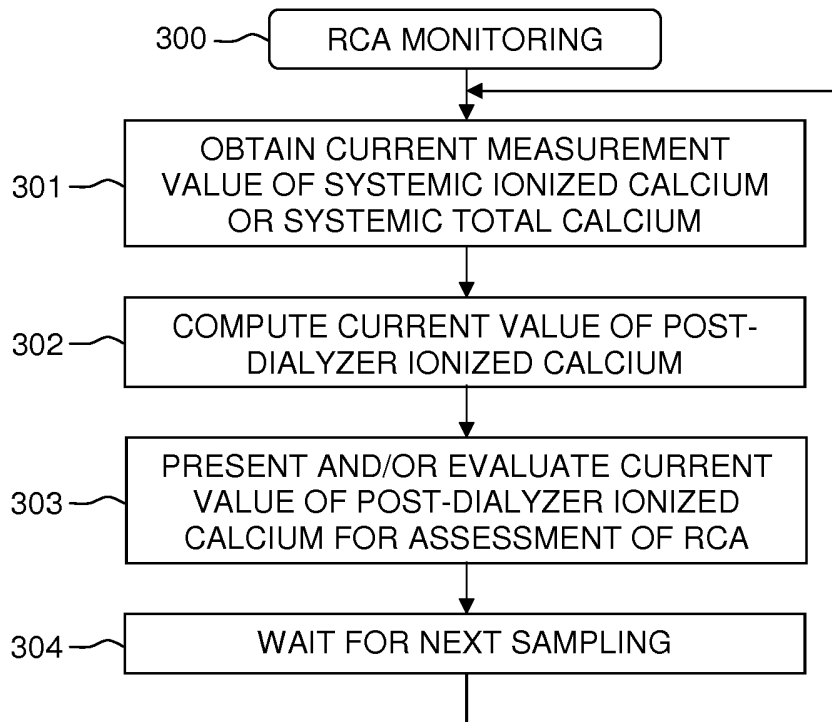


FIG. 3

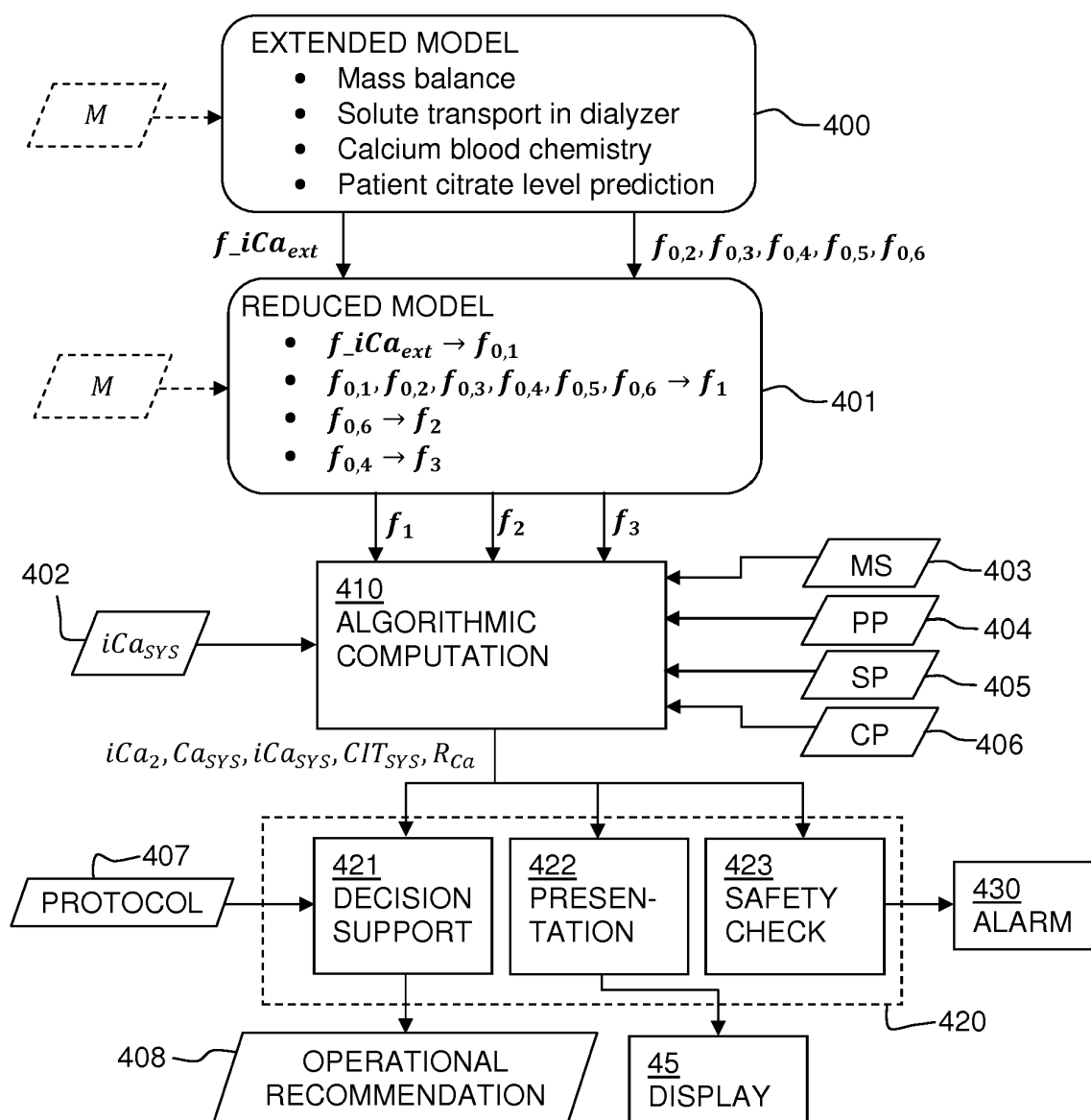


FIG. 4

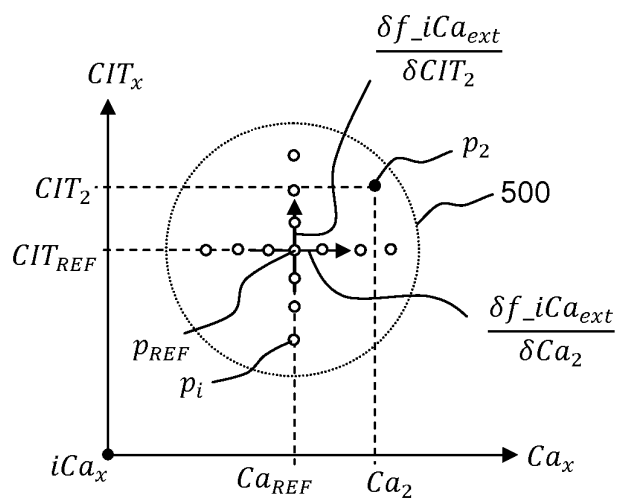


FIG. 5

MS	PP	SP	CP
Q_B	H	F_{CAL}	EQ_{CaX}
Q_D	Alb	$k_0 A_Y$	$iCIT$
Q_E	HCO_3	α_Y	iCa_{REF}
Q_{PRE}	pH	β_0	iP
Q_{POST}	W	β_1	
Q_{FIL}	fpw	β_2	
Q_{PBP}	V_D	Ca_{REF}	
D_{CIT}	K_{BODY}	CIT_{REF}	
	G_{MET}	K_C	
	CIT_0	K_{Ca}	
		CIT_{PBP}	

FIG. 6

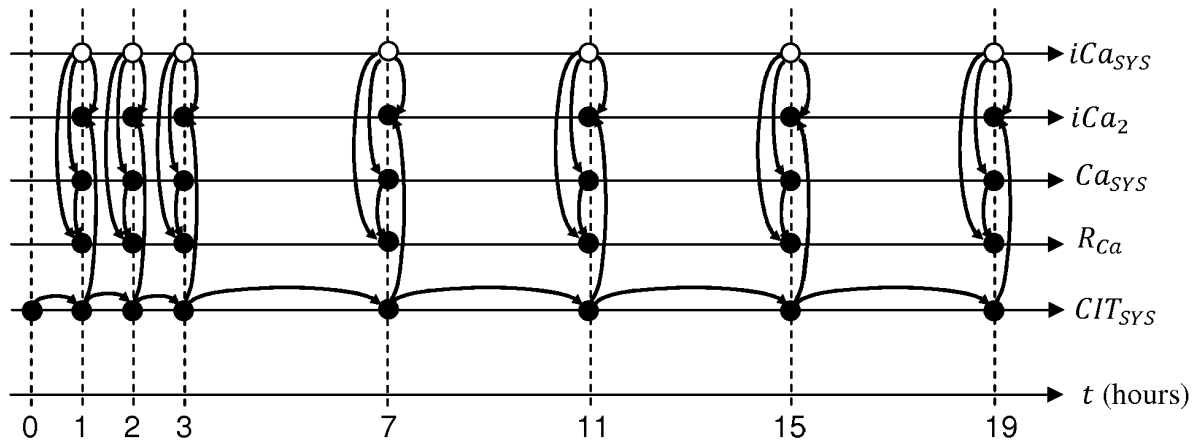


FIG. 8A

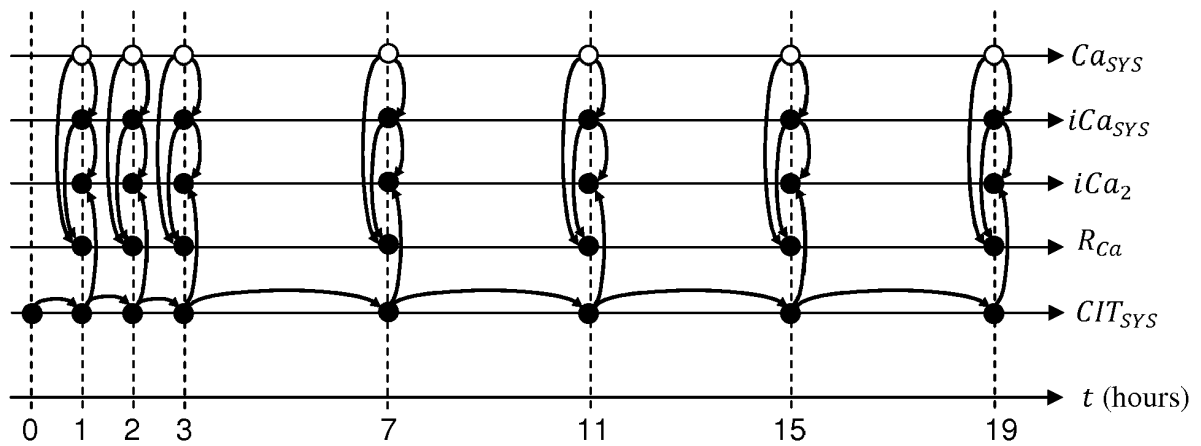


FIG. 8B

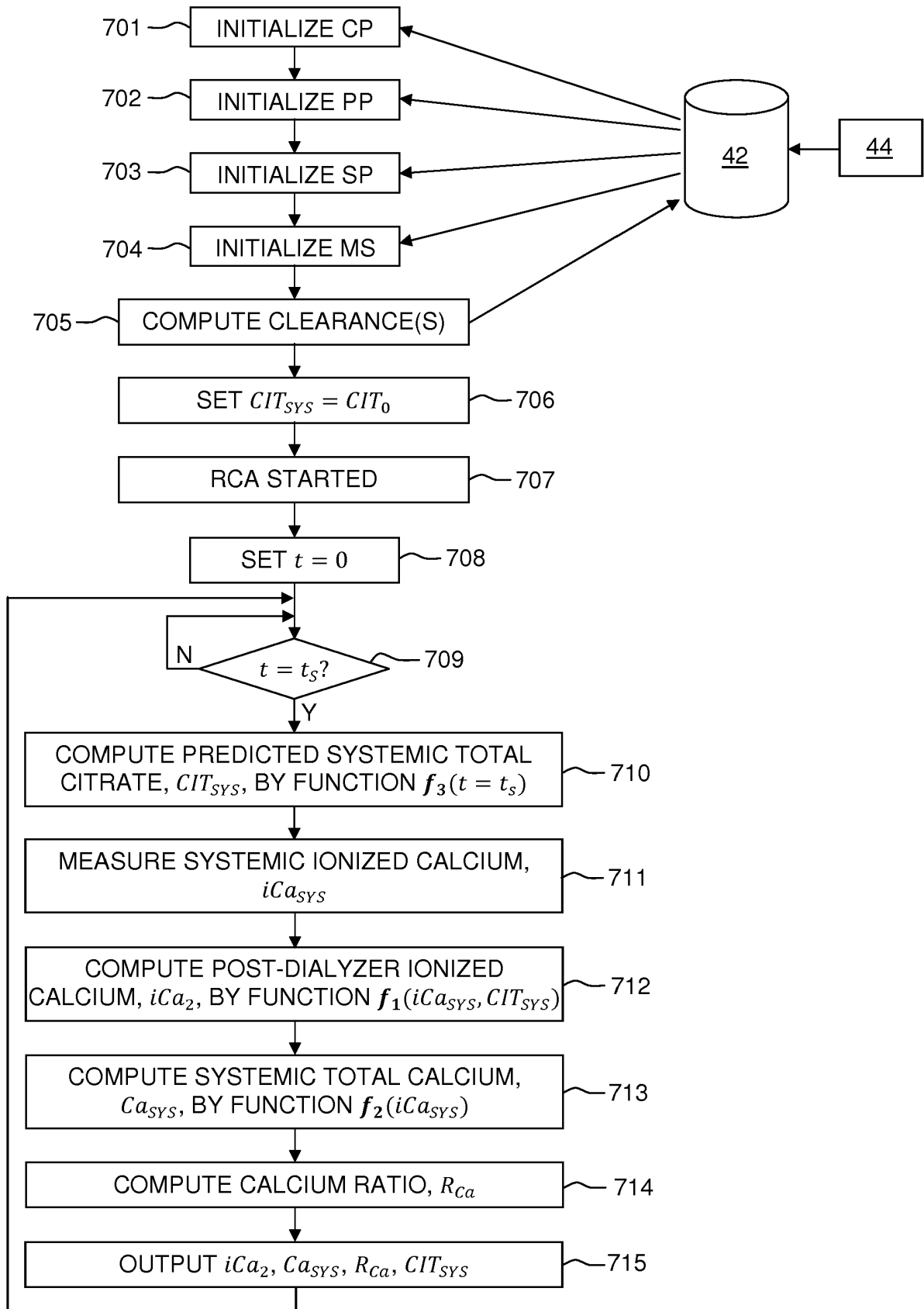


FIG. 7

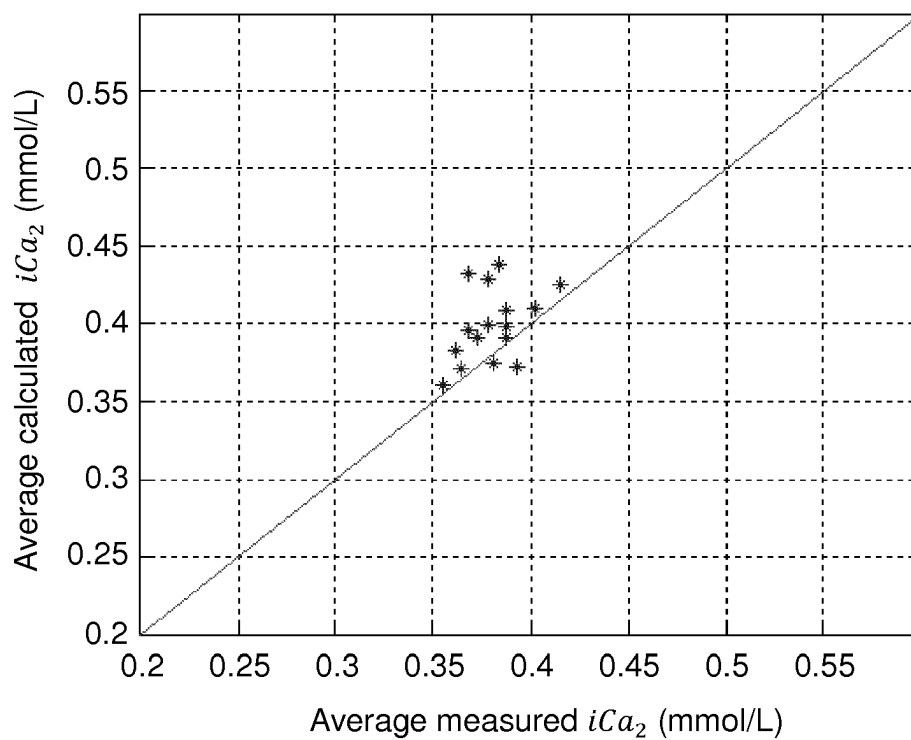


FIG. 9A

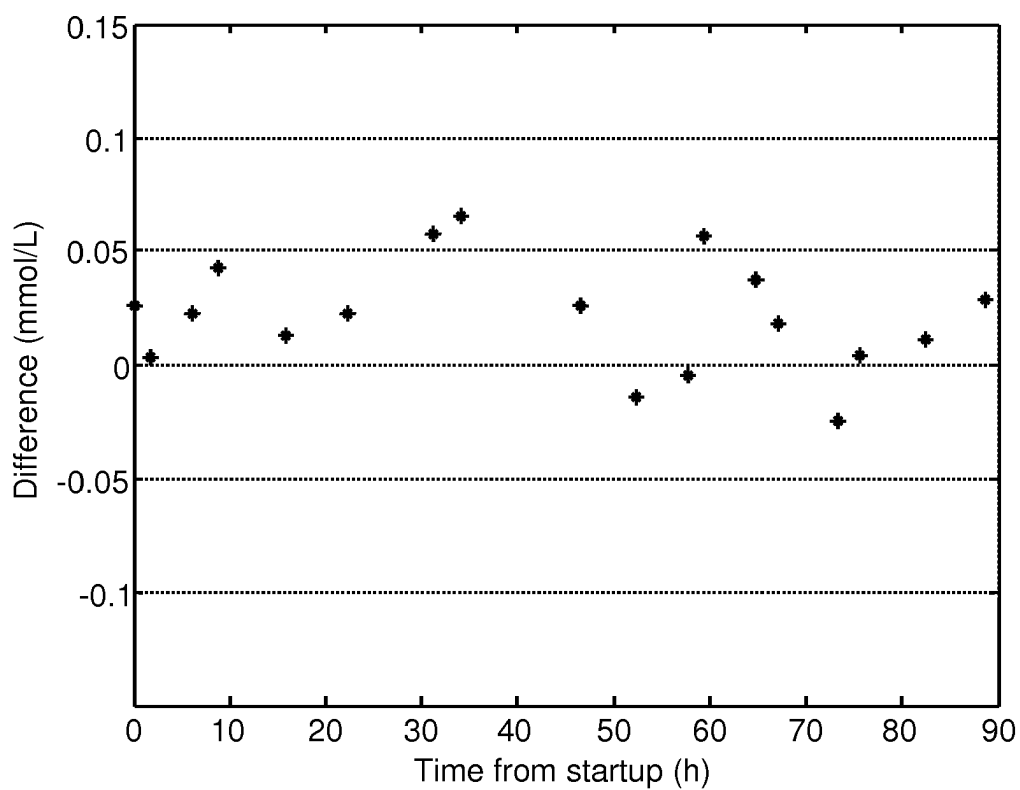


FIG. 9B

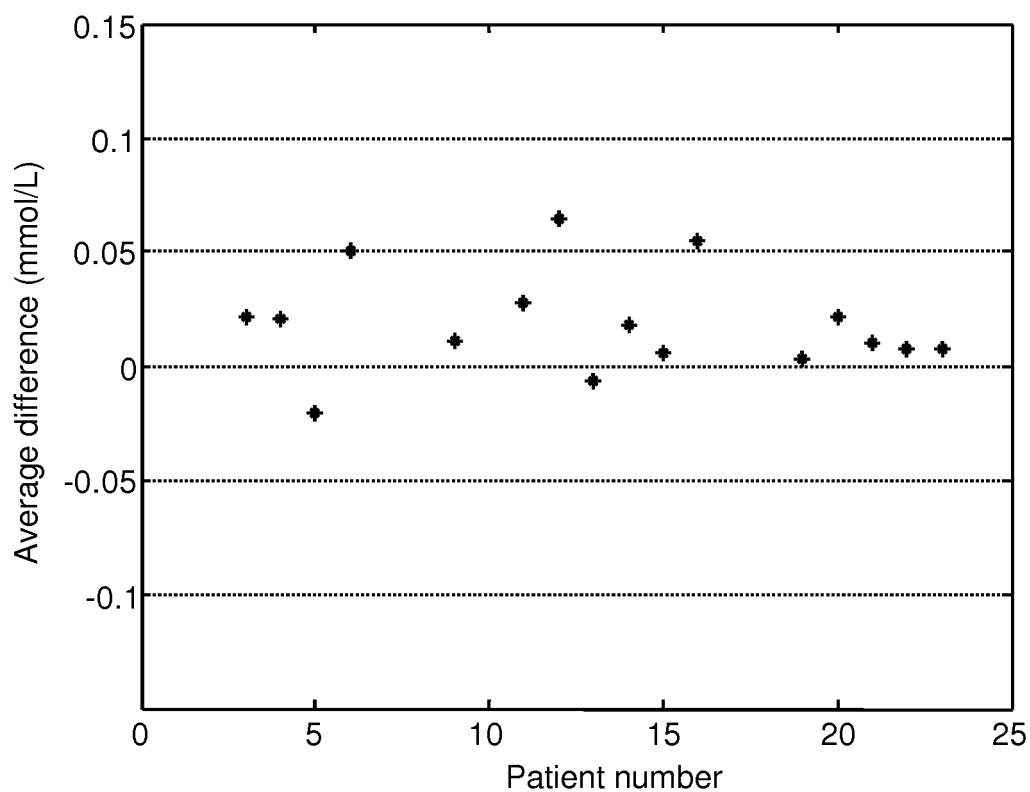


FIG. 9C

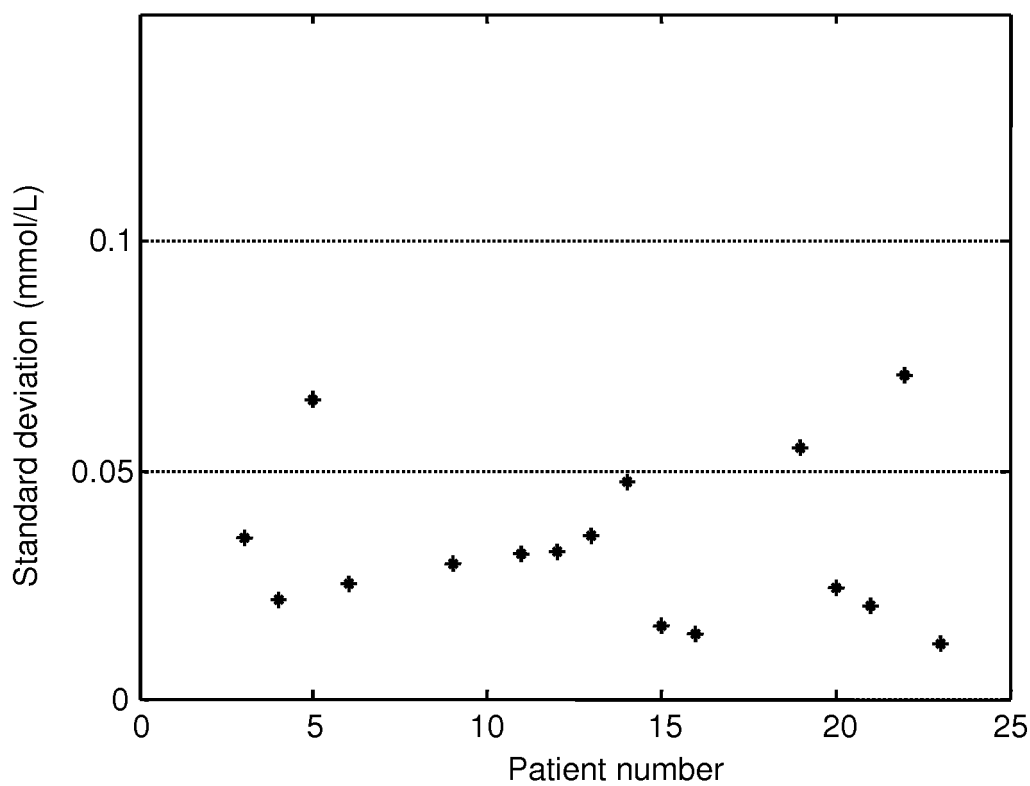


FIG. 9D

$$\begin{aligned}
iCa_2 &= f_{0,1}(Ca_2, CIT_2) = \beta_0 + \beta_1 \cdot (Ca_2 - Ca_{REF}) + \beta_2 \cdot (CIT_2 - CIT_{REF}) \\
Ca_2 &= f_{0,2}(Ca_{SYS}, H, fpw, K_{Ca}, F_{CAL}, Q_B, Q_{PRE}, Q_E, Q_D, Q_{PBP}) \\
CIT_2 &= f_{0,3}(CIT_{SYS}, H, fpw, K_{CIT}, D_{CIT}, Q_B, Q_{PRE}, Q_E, Q_D, Q_{PBP}) \\
CIT_{SYS} &= f_{0,4}(CIT_0, V_D, K_{BODY}, G_{MET}, D_{CIT}, Q_B, K_{CIT}, t) \\
K_Y &= f_{0,5}(k_0 A_Y, \alpha_Y, Q_B, Q_D, Q_{UF}) \\
Ca_{SYS} &= f_{0,6}(iCa_{SYS}, Alb, HCO_3, pH, EQ_{CaX}, iCIT, iCa_{REF}, iP) \\
iCa_{SYS} &= f_{0,7}(Ca_{SYS}, Alb, HCO_3, pH, EQ_{CaX}, iCIT, iCa_{REF}, iP) \\
iCa_{SYS} &= f_{0,7}^*(Ca_{SYS}, CIT_{SYS}) = \beta_{0,2} + \beta_{1,2} \cdot (Ca_{SYS} - Ca_{REF_2}) + \beta_{2,2} \cdot (CIT_{SYS} - CIT_{REF_2})
\end{aligned}$$

FIG. 10

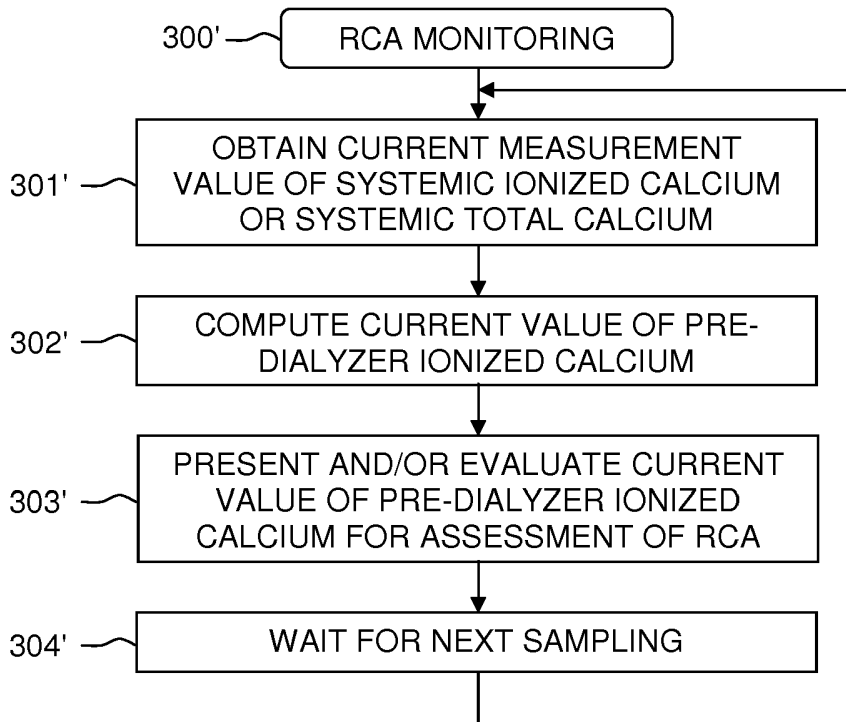


FIG. 11

REFERENCES CITED IN THE DESCRIPTION

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